RECYCLED

20

Active Ingredient Search Results from "Rx" table for query on "ciprofloxacin."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
020780		No	CIPROFLOXACIN	For Suspension; Oral	250MG/5ML	CIPRO	BAYER PHARMS
020780		Yes	CIPROFLOXACIN	For Suspension; Oral	500MG/5ML	CIPRO	BAYER PHARMS
019847		Yes	CIPROFLOXACIN	Injectable; Injection	10MG/ML	CIPRO	BAYER PHARMS
019857		Yes	CIPROFLOXACIN	Injectable; Injection	200MG/100ML	CIPRO IN DEXTROSE 5% IN PLASTIC CONTAINER	BAYER PHARMS
020369		Yes	CIPROFLOXACIN HYDROCHLORIDE	Ointment; Ophthalmic	EQ 0.3% BASE	CILOXAN	ALCON
019992		Yes	CIPROFLOXACIN HYDROCHLORIDE	Solution/Drops; Ophthalmic	EQ 0.3% BASE	CILOXAN	ALCON
019537		No	CIPROFLOXACIN HYDROCHLORIDE	Tablet; Oral	EQ 100MG BASE	CIPRO	BAYER PHARMS
019537		No	CIPROFLOXACIN HYDROCHLORIDE	Tablet; Oral	EQ 250MG BASE	CIPRO	BAYER PHARMS
019537		No	CIPROFLOXACIN HYDROCHLORIDE	Tablet; Oral	EQ 500MG BASE	CIPRO	BAYER PHARMS
019537		Yes	CIPROFLOXACIN HYDROCHLORIDE	Tablet; Oral	EQ 750MG BASE	CIPRO	BAYER PHARMS
020805		Yes	CIPROFLOXACIN HYDROCHLORIDE; HYDROCORTISONE	Suspension/Drops; Otic	EQ 0.2% BASE;1%	CIPRO HC	ALCON
021473		Yes	CIPROFLOXACIN; CIPROFLOXACIN HYDROCHLORIDE	Tablet, Extended Release; Oral	212.6MG;EQ 287.5MG BASE	CIPRO XR	BAYER PHARMS
021473		Yes	CIPROFLOXACIN; CIPROFLOXACIN HYDROCHLORIDE	Tablet; Oral	425.2MG;EQ 574.9MG BASE	CIPRO XR	BAYER PHARMS
021537		Yes	CIPROFLOXACIN; DEXAMETHASONE	Suspension/Drops; Otic	0.3%;0.1%	CIPRODEX	ALCON

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Return to Electronic Orange Book Home Page

Active Ingredient Search Results from "Rx" table for query on "levofloxacin."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
020635		Yes	LEVOFLOXACIN	Injectable; Injection	EQ 250MG /50ML (5MG/ML)	LEVAQUIN IN DEXTROSE 5% IN PLASTIC CONTAINER	ORTHO MCNEIL PHARM
020635		Yes	LEVOFLOXACIN	Injectable; Injection	EQ 500MG /20ML (25MG/ML)	LEVAQUIN	ORTHO MCNEIL PHARM
020635		Yes	LEVOFLOXACIN	Injectable; Injection	EQ 500MG 100ML/ (5MG/ML)	LEVAQUIN IN DEXTROSE 5% IN PLASTIC CONTAINER	ORTHO MCNEIL PHARM
020635		Yes	LEVOFLOXACIN	Injectable; Injection	EQ 750MG /150ML (5MG/ML)	LEVAQUIN IN DEXTROSE 5% IN PLASTIC CONTAINER	ORTHO MCNEIL PHARM
020635		Yes	LEVOFLOXACIN	Injectable; Injection	EQ 750MG /30ML (25MG/ML)	LEVAQUIN	ORTHO MCNEIL PHARM
021199		Yes	LEVOFLOXACIN	Solution/Drops; Ophthalmic	0.5%	QUIXIN	SANTEN
020634		No	LEVOFLOXACIN	Tablet; Oral	250MG	LEVAQUIN	ORTHO MCNEIL PHARM
020634		No	LEVOFLOXACIN	Tablet; Oral	500MG	LEVAQUIN	ORTHO MCNEIL PHARM
020634		Yes	LEVOFLOXACIN	Tablet; Oral	750MG	LEVAQUIN	ORTHO MCNEIL PHARM

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Return to Electronic Orange Book Home Page

Active Ingredient Search Results from "Rx" table for query on "trovafloxacin."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
020759		No	TROVAFLOXACIN MESYLATE	Tablet; Oral	EQ 100MG BASE	TROVAN	PFIZER
020759		Yes	TROVAFLOXACIN MESYLATE	Tablet; Oral	EQ 200MG BASE	TROVAN	PFIZER

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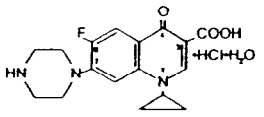
CIPRO®
(ciprofloxacin hydrochloride)
TABLETS

CIPRO®
(ciprofloxacin*)
ORAL SUSPENSION

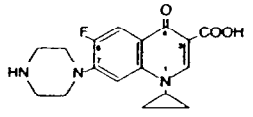
08858082 8/03

DESCRIPTION

CIPRO® (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin*) Oral Suspension are synthetic broad spectrum antimicrobial agents for oral administration. Ciprofloxacin hydrochloride, USP, a fluoroquinolone, is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. It is a faintly yellowish to light yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ and its chemical structure is as follows.



Ciprofloxacin is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its molecular weight is 331.4. It is a faintly yellowish to light yellow crystalline substance and its chemical structure is as follows.



CIPRO film-coated tablets are available in 100 mg, 250 mg, 500 mg and 750 mg (ciprofloxacin equivalent) strengths. Ciprofloxacin tablets are white to slightly yellowish. The inactive ingredients are cornstarch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol and water.

Ciprofloxacin Oral Suspension is available in 5% (5 g ciprofloxacin in 100 mL) and 10% (10 g ciprofloxacin in 100 mL) strengths. Ciprofloxacin Oral Suspension is a white to slightly yellowish suspension with strawberry flavor which may contain yellow-orange droplets. It is composed of ciprofloxacin microcapsules and diluent which are mixed prior to dispensing (See instructions for USE/HANDLING). The components of the suspension have the following compositions:

Microcapsules - ciprofloxacin, povidone, methacrylic acid copolymer, hypromellose, magnesium stearate, and Polysorbate 20.

Diluent - medium-chain triglycerides, sucrose, lecithin, water, and strawberry flavor.

* Does not comply with USP with regards to "loss on drying" and "residue on ignition"

CLINICAL PHARMACOLOGY

Absorption: Ciprofloxacin given as an oral tablet is rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Ciprofloxacin maximum serum concentrations and area under the curve are shown in the chart for the 250 mg to 1000 mg dose range.

Dose (mg)	Maximum Serum Concentration (µg/mL)	Area Under Curve (AUC) (µg•hr/mL)
250	1.2	4.8
500	2.4	11.6
750	4.3	20.2
1000	5.4	30.8

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500, or 750 mg are 0.1, 0.2, and 0.4 µg/mL, respectively. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Serum concentrations increase proportionately with doses up to 1000 mg.

A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours. A 750 mg oral dose given every 12 hours has been shown to produce an AUC at steady-state equivalent to that produced by an intravenous infusion of 400 mg given over 60 minutes every 8 hours. A 750 mg oral dose results in a C_{max} similar to that observed with a 400 mg I.V. dose. A 250 mg oral dose given every 12 hours produces an AUC equivalent to that produced by an infusion of 200 mg ciprofloxacin given every 12 hours.

Steady-state Pharmacokinetic Parameters Following Multiple Oral and I.V. Doses

Parameters	500 mg q12h, P.O.	400 mg q12h, I.V.	750 mg q12h, P.O.	400 mg q8h, I.V.
AUC (µg•hr/mL)	13.7[a]	12.7[a]	31.6[b]	32.9[c]
C_{max} (µg/mL)	2.97	4.56	3.59	4.07

[a] AUC_{0-12h}
[b] AUC 24h=AUC_{0-12h} x 2
[c] AUC 24h=AUC_{0-8h} x 3

Distribution: The binding of ciprofloxacin to serum proteins is 20 to 40% which is not likely to be high enough to cause significant protein binding interactions with other drugs.

After oral administration, ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug diffuses into the cerebrospinal fluid (CSF), however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humors of the eye.

Metabolism: Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin.

Excretion: The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. After a 250 mg oral dose, urine concentrations of ciprofloxacin usually exceed 200 µg/mL during the first two hours and are approximately 30 µg/mL at 8 to 12 hours after dosing. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Co-administration of probenecid with ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1 to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20 to 35% of an oral dose is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

With oral administration, a 500 mg dose, given as 10 mL of the 5% CIPRO Suspension (containing 250 mg ciprofloxacin/5mL) is bioequivalent to the 500 mg tablet. A 10 mL volume of the 5% CIPRO Suspension (containing 250 mg ciprofloxacin/5mL) is bioequivalent to a 5 mL volume of the 10% CIPRO Suspension (containing 500 mg ciprofloxacin/5mL).

Drug-drug Interactions: When CIPRO Tablet is given concomitantly with food there is a delay in the absorption of the drug, resulting in peak concentrations that occur closer to 2 hours after dosing rather than 1 hour whereas there is no delay observed when CIPRO Suspension is given with food. The overall absorption of CIPRO Tablet or CIPRO Suspension, however, is not substantially affected. The pharmacokinetics of ciprofloxacin given as the suspension are also not affected by food. Concurrent administration of antacids containing magnesium hydroxide or aluminum hydroxide may reduce the bioavailability of ciprofloxacin by as much as 90%. (See **PRECAUTIONS.**)

The serum concentrations of ciprofloxacin and metronidazole were not altered when these two drugs were given concomitantly.

Concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of paraxanthine after caffeine administration. (See **PRECAUTIONS.**)

Special Populations: Pharmacokinetic studies of the oral (single dose) and intravenous (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (> 65 years) as compared to young adults. Although the C_{max} is increased 16-40%, the increase in mean AUC is approximately 30%, and can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant. (See **PRECAUTIONS: Geriatric Use.**)

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Dosage adjustments may be required. (See **DOSAGE AND ADMINISTRATION.**)

In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated.

Microbiology: Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. *In vitro* resistance to ciprofloxacin develops slowly by multiple step mutations.

Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for CIPRO (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin*) 5% and 10% Oral Suspension.

Aerobic gram-positive microorganisms

Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus aureus (methicillin-susceptible strains only)
Staphylococcus epidermidis (methicillin-susceptible strains only)
Staphylococcus saprophyticus
Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes

Aerobic gram-negative microorganisms

Campylobacter jejuni
Citrobacter diversus
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Salmonella typhi
Serratia marcescens
Shigella boydii
Shigella dysenteriae
Shigella flexneri
Shigella sonnei

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker (see **INDICATIONS AND USAGE** and **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**).

The following *in vitro* data are available, **but their clinical significance is unknown.**

Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 µg/mL or less against most (≥ 90%) strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms

Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus pneumoniae (penicillin-resistant strains only)

Aerobic gram-negative microorganisms

Acinetobacter lwoffi
Aeromonas hydrophila
Edwardsiella tarda
Enterobacter aerogenes
Klebsiella oxytoca
Legionella pneumophila
Pasteurella multocida
Salmonella enteritidis
Vibrio cholerae
Vibrio parahaemolyticus
Vibrio vulnificus
Yersinia enterocolitica

Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

Susceptibility Tests

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*:[a]

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)
2	Intermediate (I)
≥ 4	Resistant (R)

[a] These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*:[b]

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)

[b] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium[1].

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Neisseria gonorrhoeae*:[c]

MIC (µg/mL)	Interpretation
≤ 0.06	Susceptible (S)
0.12 – 0.5	Intermediate (I)
≥ 1	Resistant (R)

[c] This interpretive standard is applicable only to agar dilution test with GC agar base and 1% defined growth supplement.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard ciprofloxacin powder should provide the following MIC values:

Organism		MIC (µg/mL)
E. faecalis	ATCC 29212	0.25 – 2.0
E. coli	ATCC 25922	0.004 – 0.015
H. influenzae[a]	ATCC 49247	0.004 – 0.03
N. gonorrhoeae[b]	ATCC 49226	0.001 – 0.008
P. aeruginosa	ATCC 27853	0.25 – 1.0
S. aureus	ATCC 29213	0.12 – 0.5

[a] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM)[1].

[b] This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base and 1% defined growth supplement.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg ciprofloxacin disk should be interpreted according to the following criteria.

For testing aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*[a]:

Zone Diameter (mm)	Interpretation
≥ 21	Susceptible (S)
16 – 20	Intermediate (I)
≤ 15	Resistant (R)

[a] These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[b]:

Zone Diameter (mm)	Interpretation
≥ 21	Susceptible (S)

[b] This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)[2].

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Neisseria gonorrhoeae*[c]:

Zone Diameter (mm)	Interpretation
≥ 41	Susceptible (S)
28 – 40	Intermediate (I)
≤ 27	Resistant (R)

[c] This zone diameter standard is applicable only to disk diffusion tests with GC agar base and 1% defined growth supplement. Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ciprofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-µg ciprofloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

Organism		Zone Diameter (mm)
E. coli	ATCC 25922	30 – 40
H. influenzae[a]	ATCC 49247	34 – 42
N. gonorrhoeae[b]	ATCC 49226	48 – 58
P. aeruginosa	ATCC 27853	25 – 33
S. aureus	ATCC 25923	22 – 30

[a] These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM)[2].

[b] These quality control limits are applicable only to tests conducted with *N. gonorrhoeae* ATCC 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement.

INDICATIONS AND USAGE

CIPRO is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, or *Enterococcus faecalis*.

Acute Uncomplicated Cystitis in females caused by *Escherichia coli* or *Staphylococcus saprophyticus*. (See **DOSAGE AND ADMINISTRATION**.)

Chronic Bacterial Prostatitis caused by *Escherichia coli* or *Proteus mirabilis*.

Lower Respiratory Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Streptococcus pneumoniae*. Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae*.

Acute Sinusitis caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Moraxella catarrhalis*.

Skin and Skin Structure Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (methicillin-susceptible), *Staphylococcus epidermidis*, or *Streptococcus pyogenes*.

Bone and Joint Infections caused by *Enterobacter cloacae*, *Serratia marcescens*, or *Pseudomonas aeruginosa*.

Complicated Intra-Abdominal Infections (used in combination with metronidazole) caused by *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, or *Bacteroides fragilis*. (See **DOSAGE AND ADMINISTRATION**.)

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*, *Shigella boydii*[1], *Shigella dysenteriae*, *Shigella flexneri* or *Shigella sonnei*[1] when antibacterial therapy is indicated.

Typhoid Fever (Enteric Fever) caused by *Salmonella typhi*.

NOTE: The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier state has not been demonstrated.

Uncomplicated cervical and urethral gonorrhea due to *Neisseria gonorrhoeae*.

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.[4] (See also, **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**).

[1] Although treatment of infections due to this organism in this organ system demonstrated a clinically significant outcome, efficacy was studied in fewer than 10 patients.

If anaerobic organisms are suspected of contributing to the infection, appropriate therapy should be administered. Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with CIPRO may be initiated before results of these tests are known; once results become available appropriate therapy should be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

CIPRO (ciprofloxacin hydrochloride) is contraindicated in persons with a history of hypersensitivity to ciprofloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (LESS THAN 18 YEARS OF AGE), – EXCEPT FOR USE IN INHALATIONAL ANTHRAX (POST-EXPOSURE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy, and Nursing Mothers subsections.) The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY**.)

Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). (See **PRECAUTIONS: General, Information for Patients, Drug Interactions** and **ADVERSE REACTIONS**.)

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND THEOPHYLLINE. These reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure. Although similar serious adverse effects have been reported in patients receiving theophylline alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been rarely reported in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with ciprofloxacin and other quinolones. Post-marketing surveillance reports indicate that the risk may be increased in patients receiving concomitant corticosteroids, especially in the elderly. Ciprofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon.

Ciprofloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high dose for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with ciprofloxacin should have a follow-up serologic test for syphilis after three months.

PRECAUTIONS

General: Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals, which is usually alkaline. (See **ANIMAL PHARMACOLOGY**.) Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Alkalinity of the urine should be avoided in patients receiving ciprofloxacin. Patients should be well hydrated to prevent the formation of highly concentrated urine.

Quinolones, including ciprofloxacin, may also cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia. (See **WARNINGS, Information for Patients**, and **Drug Interactions**.)

Alteration of the dosage regimen is necessary for patients with impairment of renal function. (See **DOSAGE AND ADMINISTRATION**.)

Moderate to severe phototoxicity manifested as an exaggerated sunburn reaction has been observed in patients who are exposed to direct sunlight while receiving some members of the quinolone class of drugs. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Information for Patients:

Patients should be advised:

- that ciprofloxacin may be taken with or without meals and to drink fluids liberally. As with other quinolones, concurrent administration of ciprofloxacin with magnesium/aluminum antacids, or sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder, or with other products containing calcium, iron or zinc should be avoided. Ciprofloxacin may be taken two hours before or six hours after taking these products. Ciprofloxacin should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone since absorption of ciprofloxacin may be significantly reduced; however, ciprofloxacin may be taken with a meal that contains these products.
- that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.
- to avoid excessive sunlight or artificial ultraviolet light while receiving ciprofloxacin and to discontinue therapy if phototoxicity occurs.
- to discontinue treatment, rest and refrain from exercise, and inform their physician if they experience pain, inflammation, or rupture of a tendon.
- that ciprofloxacin may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.
- that ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking quinolones.
- that convulsions have been reported in patients receiving quinolones, including ciprofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

Drug Interactions: As with some other quinolones, concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline related adverse reactions. (See **WARNINGS**.) If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Some quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life.

Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc may substantially decrease its absorption, resulting in serum and urine levels considerably lower than desired. (See **DOSAGE AND ADMINISTRATION** for concurrent administration of these agents with ciprofloxacin.)

Histamine H_2 receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin.

The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has, on rare occasions, resulted in severe hypoglycemia.

Some quinolones, including ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Quinolones, including ciprofloxacin, have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate-associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Metoclopramide accelerates the absorption of oral ciprofloxacin, resulting in shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Animal studies have shown that the combination of very high doses of quinolones and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below:

- Salmonella/Microsome Test (Negative)
- *E. coli* DNA Repair Assay (Negative)
- Mouse Lymphoma Cell Forward Mutation Assay (Positive)
- Chinese Hamster V_{79} Cell HGPRT Test (Negative)
- Syrian Hamster Embryo Cell Transformation Assay (Negative)
- *Saccharomyces cerevisiae* Point Mutation Assay (Negative)
- *Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative)
- Rat Hepatocyte DNA Repair Assay (Positive)

Thus, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test systems gave negative results:

- Rat Hepatocyte DNA Repair Assay
- Micronucleus Test (Mice)
- Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in mice and rats have been completed. After daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks; while concurrently being administered ciprofloxacin. The time to development of the first skin tumors was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon mg/m²), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumors ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones.[3]

In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (0.8 times the highest recommended human dose of 1200 mg based upon body surface area) revealed no evidence of impairment.

Pregnancy: Teratogenic Effects. Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS – the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data=fair), but the data are insufficient to state that there is no risk.[2]

A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.[3] In utero exposure to fluoroquinolones during

embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group (background incidence of major malformations is 1-5%). Rates of spontaneous abortions, prematurity and low birth weight did not differ between the groups and there were no clinically significant musculoskeletal dysfunctions up to one year of age in the ciprofloxacin exposed children.

Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure (93% first trimester exposures).[3] There were 70 ciprofloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones overall were both within background incidence ranges. No specific patterns of congenital abnormalities were found. The study did not reveal any clear adverse reactions due to in utero exposure to ciprofloxacin.

No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women exposed to ciprofloxacin during pregnancy.[1,3] However these small postmarketing epidemiology studies, of which most experience is from short term first trimester exposure are insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother (see **WARNINGS**).

Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. (See **WARNINGS**.)

Nursing Mothers: Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin absorbed by the nursing infant is unknown. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients and adolescents less than 18 years of age have not been established, except for use in inhalational anthrax (post-exposure). Ciprofloxacin causes arthropathy in juvenile animals. (See **WARNINGS**.)

For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to pediatric patients is appropriate. For information regarding pediatric dosing in inhalational anthrax (post-exposure), see **DOSAGE AND ADMINISTRATION** and **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**.

Short-term safety data from a single trial in pediatric cystic fibrosis patients are available. In a randomized, double-blind clinical trial for the treatment of acute pulmonary exacerbations in cystic fibrosis patients (ages 5-17 years), 67 patients received ciprofloxacin I.V. 10 mg/kg/dose q8h for one week followed by ciprofloxacin tablets 20 mg/kg/dose q12h to complete 10-21 days treatment and 62 patients received the combination of ceftazidime I.V. 50 mg/kg/dose q8h and tobramycin I.V. 3 mg/kg/dose q8h for a total of 10-21 days. Patients less than 5 years of age were not studied. Safety monitoring in the study included periodic range of motion examinations and gait assessments by treatment-blinded examiners. Patients were followed for an average of 23 days after completing treatment (range 0-93 days). This study was not designed to determine long term effects and the safety of repeated exposure to ciprofloxacin.

In the study, injection site reactions were more common in the ciprofloxacin group (24%) than in the comparison group (8%). Other adverse events were similar in nature and frequency between treatment arms. Musculoskeletal adverse events were reported in 22% of the patients in the ciprofloxacin group and 21% in the comparison group. Decreased range of motion was reported in 12% of the subjects in the ciprofloxacin group and 16% in the comparison group. Arthralgia was reported in 10% of the patients in the ciprofloxacin group and 11% in the comparison group. One of sixty-seven patients developed arthritis of the knee nine days after a ten day course of treatment with ciprofloxacin. Clinical symptoms resolved, but an MRI showed knee effusion without other abnormalities eight months after treatment. However, the relationship of this event to the patient's course of ciprofloxacin can not be definitively determined, particularly since patients with cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease process.

Geriatric Use: In a retrospective analysis of 23 multiple-dose controlled clinical trials of ciprofloxacin encompassing over 3500 ciprofloxacin treated patients, 25% of patients were greater than or equal to 65 years of age and 10% were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals on any drug therapy cannot be ruled out. Ciprofloxacin is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. No alteration of dosage is necessary for patients greater than 65 years of age with normal renal function. However, since some older individuals experience reduced renal function by virtue of their advanced age, care should be taken in dose selection for elderly patients, and renal function monitoring may be useful in these patients. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**.)

ADVERSE REACTIONS

During clinical investigations with oral and parenteral ciprofloxacin 49,038 patients received courses of the drug. Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment. Ciprofloxacin was discontinued because of an adverse event in 1.0% of orally treated patients.

The most frequently reported drug related events, from clinical trials of all formulations, all dosages, all drug-therapy durations, and for all indications of ciprofloxacin therapy were nausea (2.5%), diarrhea (1.6%), liver function tests abnormal (1.3%), vomiting (1.0%), and rash (1.0%).

Additional medically important events that occurred in less than 1% of ciprofloxacin patients are listed below:

BODY AS A WHOLE: headache, abdominal pain/discomfort, foot pain, pain, pain in extremities, injection site reaction (ciprofloxacin intravenous)

CARDIOVASCULAR: palpitation, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis, phlebitis, tachycardia, migraine, hypotension

CENTRAL NERVOUS SYSTEM: restlessness, dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia, abnormal gait, grand mal convulsion

GASTROINTESTINAL: painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding, cholestatic jaundice, hepatitis

HEMIC/LYMPHATIC: lymphadenopathy, petechia

METABOLIC/NUTRITIONAL: amylase increase, lipase increase

MUSCULOSKELETAL: arthralgia or back pain, joint stiffness, achiness, neck or chest pain, flare up of gout

RENAL/UROGENITAL: interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis, breast pain

RESPIRATORY: dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, pulmonary embolism

SKIN/HYPERSENSITIVITY: pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum, sweating

SPECIAL SENSES: blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste, chromatopsia

In several instances nausea, vomiting, tremor, irritability, or palpitation were judged by investigators to be related to elevated serum levels of theophylline possibly as a result of drug interaction with ciprofloxacin.

In randomized, double-blind controlled clinical trials comparing ciprofloxacin tablets (500 mg BID) to cefuroxime axetil (250 mg - 500 mg BID) and to clarithromycin (500 mg BID) in patients with respiratory tract infections, ciprofloxacin demonstrated a CNS adverse event profile comparable to the control drugs.

Post-Marketing Adverse Events: The following adverse events have been reported from worldwide marketing experience with quinolones, including ciprofloxacin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, or (3) strength of causal connection to the drug.

Agitation, agranulocytosis, albuminuria, anaphylactic reactions, anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, fixed eruption, flatulence, glucose elevation (blood), hemolytic anemia, hepatic failure, hepatic necrosis, hyperesthesia, hypertonia, hypesthesia, hypotension (postural), jaundice, marrow depression (life threatening), methemoglobinemia, monoliasis (oral, gastrointestinal, vaginal), myalgia, myasthenia, myasthenia gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis, pancytopenia (life threatening or fatal outcome), phenyton alteration (serum), potassium elevation (serum), prothrombin time prolongation or decrease, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.), psychosis (toxic), renal calculi, serum sickness like reaction, Stevens-Johnson syndrome, taste loss, tendinitis, tendon rupture, toxic epidermal necrolysis, triglyceride elevation (serum), twitching, vaginal candidiasis, and vasculitis. (See **PRECAUTIONS**.)

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship are listed below:

Hepatic – Elevations of ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%)

Hematologic – Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated blood platelets (0.1%), pancytopenia (0.1%)

Renal – Elevations of serum creatinine (1.1%), BUN (0.9%). CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.

Other changes occurring in less than 0.1% of courses were elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, leukocytosis.

OVERDOSAGE

In the event of acute overdosage, reversible renal toxicity has been reported in some cases. The stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment, including monitoring of renal function and administration of magnesium or calcium containing antacids which can reduce the absorption of ciprofloxacin. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (< 10%) is removed from the body after hemodialysis or peritoneal dialysis.

Single doses of ciprofloxacin were relatively non-toxic via the oral route of administration in mice, rats, and dogs. No deaths occurred within a 14-day post treatment observation period at the highest oral doses tested, up to 5000 mg/kg in either rodent species, or up to 2500 mg/kg in the dog. Clinical signs observed included hypoactivity and cyanosis in both rodent species and severe vomiting in dogs. In rabbits, significant mortality was seen at doses of ciprofloxacin > 2500 mg/kg. Mortality was delayed in these animals, occurring 10-14 days after dosing.

In mice, rats, rabbits and dogs, significant toxicity including tonic/clonic convulsions was observed at intravenous doses of ciprofloxacin between 125 and 300 mg/kg.

DOSAGE AND ADMINISTRATION

CIPRO Tablets and Oral Suspension should be administered orally as described in the Dosage Guidelines table.

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defense mechanisms, and the status of renal function and hepatic function.

The duration of treatment depends upon the severity of infection. The usual duration is 7 to 14 days; however, for severe and complicated infections more prolonged therapy may be required. Ciprofloxacin should be administered at least 2 hours before or 6 hours after magnesium/aluminum antacids, or sucralfate. Videx® (didanosine) chewable/buffered tablets or pediatric powder for oral solution, or other products containing calcium, iron or zinc.

DOSAGE GUIDELINES

Infection	Type or Severity	Unit Dose	Frequency	Usual Durations†
Urinary Tract	Acute Uncomplicated	100 mg or 250 mg	q 12 h	3 Days
	Mild/Moderate	250 mg	q 12 h	7 to 14 Days
	Severe/Complicated	500 mg	q 12 h	7 to 14 Days
Chronic Bacterial Prostatitis	Mild/Moderate	500 mg	q 12 h	28 Days
Lower Respiratory Tract	Mild/Moderate	500 mg	q 12 h	7 to 14 days
	Severe/Complicated	750 mg	q 12 h	7 to 14 days
Acute Sinusitis	Mild/Moderate	500 mg	q 12 h	10 days
Skin and Skin Structure	Mild/Moderate	500 mg	q 12 h	7 to 14 Days
	Severe/Complicated	750 mg	q 12 h	7 to 14 Days
Bone and Joint	Mild/Moderate	500 mg	q 12 h	≥ 4 to 6 weeks
	Severe/Complicated	750 mg	q 12 h	≥ 4 to 6 weeks
Intra-Abdominal*	Complicated	500 mg	q 12 h	7 to 14 Days
Infectious Diarrhea	Mild/Moderate/Severe	500 mg	q 12 h	5 to 7 Days
Typhoid Fever	Mild/Moderate	500 mg	q 12 h	10 Days
Urethral and Cervical Gonococcal Infections	Uncomplicated	250 mg	single dose	single dose
Inhalational anthrax (post-exposure)**	Adult	500 mg	q 12 h	60 Days
	Pediatric	15 mg/kg per dose, not to exceed 500 mg per dose	q 12 h	60 Days

* used in conjunction with metronidazole

† Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared, except for inhalational anthrax (post-exposure).

** Drug administration should begin as soon as possible after suspected or confirmed exposure.

This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit.[4] For a discussion of ciprofloxacin serum concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**.

Patients whose therapy is started with CIPRO I.V. may be switched to CIPRO Tablets or Oral Suspension when clinically indicated at the discretion of the physician (See **CLINICAL PHARMACOLOGY** and table below for the equivalent dosing regimens).

Equivalent AUC Dosing Regimens

Cipro Oral Dosage	Equivalent Cipro I.V. Dosage
250 mg Tablet q 12 h	200 mg I.V. q 12 h
500 mg Tablet q 12 h	400 mg I.V. q 12 h
750 mg Tablet q 12 h	400 mg I.V. q 8 h

Impaired Renal Function: Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. These alternative pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction. The following table provides dosage guidelines for use in patients with renal impairment; however, monitoring of serum drug levels provides the most reliable basis for dosage adjustment.

RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance (mL/min)	Dose
> 50	See Usual Dosage.
30 – 50	250 – 500 mg q 12 h
5 – 29	250 – 500 mg q 18 h
Patients on hemodialysis or Peritoneal dialysis)	250 – 500 mg q 24 h (after dialysis)

When only the serum creatinine concentration is known, the following formula may be used to estimate creatinine clearance.

$$\text{Men. Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men.

The serum creatinine should represent a steady state of renal function.

In patients with severe infections and severe renal impairment, a unit dose of 750 mg may be administered at the intervals noted above, however, patients should be carefully monitored and the serum ciprofloxacin concentration should be measured periodically. Peak concentrations (1 – 2 hours after dosing) should generally range from 2 to 4 µg/mL.

For patients with changing renal function or for patients with renal impairment and hepatic insufficiency, measurement of serum concentrations of ciprofloxacin will provide additional guidance for adjusting dosage.

HOW SUPPLIED

CIPRO (ciprofloxacin hydrochloride) Tablets are available as round, slightly yellowish film-coated tablets containing 100 mg or 250 mg ciprofloxacin. The 100 mg tablet is coded with the word "CIPRO" on one side and "100" on the reverse side. The 250 mg tablet is coded with the word "CIPRO" on one side and "250" on the reverse side. CIPRO is also available as capsule shaped, slightly yellowish film-coated tablets containing 500 mg or 750 mg ciprofloxacin. The 500 mg tablet is coded with the word "CIPRO" on one side and "500" on the reverse side. The 750 mg tablet is coded with the word "CIPRO" on one side and "750" on the reverse side. CIPRO 250 mg, 500 mg, and 750 mg are available in bottles of 50, 100, and Unit Dose packages of 100. The 100 mg strength is available only as CIPRO Cystitis pack containing 6 tablets for use only in female patients with acute uncomplicated cystitis.

	Strength	NDC Code	Tablet Identification
Bottles of 50:	750 mg	NDC 0026-8514-50	CIPRO 750
Bottles of 100:	250 mg	NDC 0026-8512-51	CIPRO 250
	500 mg	NDC 0026-8513-51	CIPRO 500
Unit Dose Package of 100:	250 mg	NDC 0026-8512-48	CIPRO 250
	500 mg	NDC 0026-8513-48	CIPRO 500
	750 mg	NDC 0026-8514-48	CIPRO 750
Cystitis Package of 6:	100 mg	NDC 0026-8511-06	CIPRO 100

Store below 30°C (86°F).

CIPRO Oral Suspension is supplied in 5% and 10% strengths. The drug product is composed of two components (microcapsules containing the active ingredient and diluent) which must be mixed by the pharmacist. See Instructions To The Pharmacist For Use/Handling.

Strengths	Total volume after reconstitution	Ciprofloxacin Concentration	Ciprofloxacin contents per bottle	NDC Code
5%	100 mL	250 mg/5 mL	5,000 mg	0026-8551-36
10%	100 mL	500 mg/5 mL	10 000 mg	0026-8553-36

Microcapsules and diluent should be stored below 25°C (77°F) and protected from freezing.

Reconstituted product may be stored below 30°C (86°F) for 14 days. Protect from freezing. A teaspoon is provided for the patient.

ANIMAL PHARMACOLOGY

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See **WARNINGS.**) Damage of weight bearing joints was observed in juvenile dogs and rats. In young beagles, 100 mg/kg ciprofloxacin, given daily for 4 weeks, caused degenerative articular changes of the knee joint. At 30 mg/kg, the effect on the joint was minimal. In a subsequent study in beagles, removal of weight bearing from the joint reduced the lesions but did not totally prevent them.

Crystalluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed with ciprofloxacin. This is primarily related to the reduced solubility of ciprofloxacin under alkaline conditions, which predominate in the urine of test animals, in man, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria without nephropathy has been noted after single oral doses as low as 5 mg/kg. After 6 months of intravenous dosing at 10 mg/kg/day, no nephropathological changes were noted; however nephropathy was observed after dosing at 20 mg/kg/day for the same duration.

In dogs, ciprofloxacin at 3 and 10 mg/kg by rapid I.V. injection (15 sec.) produces pronounced hypotensive effects. These effects are considered to be related to histamine release, since they are partially antagonized by pyrilamine, an antihistamine. In rhesus monkeys, rapid I.V. injection also produces hypotension but the effect in this species is inconsistent and less pronounced.

In mice, concomitant administration of nonsteroidal anti-inflammatory drugs such as phenylbutazone and indomethacin with quinolones has been reported to enhance the CNS stimulatory effect of quinolones.

Ocular toxicity seen with some related drugs has not been observed in ciprofloxacin-treated animals.

CLINICAL STUDIES

Uncomplicated Cystitis

Two double-blind, controlled clinical studies of acute uncomplicated cystitis in women were performed in the U.S. At the 5-9 day post-therapy follow-up visit, the clinical resolution rates in the first study, which compared ciprofloxacin 100 mg BID for 3 days to ciprofloxacin 250 mg BID for 7 days, were 87% (82/94) and 94%, (81/86), respectively. For *E. coli*, the bacteriological eradication rates for the first study were 91% (64/70) in the ciprofloxacin 100 mg regimen and 97% (67/69) in the ciprofloxacin 250 mg regimen. The second study's bacteriological eradication rates were 95% (117/123) for the ciprofloxacin 100 mg regimen and 98% (103/105) for the control regimen. Pooled eradication rates for the ciprofloxacin 100 mg treatment arms were 100% (16/16) for *S. saprophyticus*.

INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and pediatric patients receiving oral and intravenous regimens. (See **DOSAGE AND ADMINISTRATION.**) Ciprofloxacin pharmacokinetics have been evaluated in various human populations. The mean peak serum concentration achieved at steady-state in human adults receiving 500 mg orally every 12 hours is 2.97 µg/mL, and 4.56 µg/mL following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady-state for both of these regimens is 0.2 µg/mL. In a study of 10 pediatric patients between 6 and 16 years of age, the mean peak plasma concentration achieved is 8.3 µg/mL and trough concentrations range from 0.09 to 0.26 µg/mL, following two 30-minute intravenous infusions of 10 mg/kg administered 12 hours apart. After the second intravenous infusion patients switched to 15 mg/kg orally every 12 hours achieve a mean peak concentration of 3.6 µg/mL after the initial oral dose. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to pediatric patients are limited. (For additional information, see **PRECAUTIONS, Pediatric Use.**) Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.[4]

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD_{50} (~5.5 x 10^5 spores (range 5-30 LD_{50}) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 µg/mL. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady-state ranged from 0.98 to 1.69 µg/mL. Mean steady-state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 µg/mL[5]. Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly lower (1/9), compared to the placebo group (9/10) [p= 0.001]. The one ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period.[6]

Instructions To The Pharmacist For Use/Handling Of CIPRO Oral Suspension:

CIPRO Oral Suspension is supplied in 5% (5 g ciprofloxacin in 100 mL) and 10% (10 g ciprofloxacin in 100 mL) strengths. The drug product is composed of two components (microcapsules and diluent) which must be combined prior to dispensing.

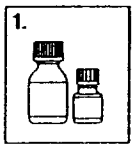
One teaspoonful (5 mL) of 5% ciprofloxacin oral suspension = 250 mg of ciprofloxacin.

One teaspoonful (5 mL) of 10% ciprofloxacin oral suspension = 500 mg of ciprofloxacin.

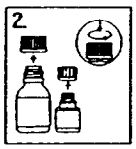
Appropriate Dosing Volumes of the Oral Suspensions:

Dose	5%	10%
250 mg	5 mL	2.5 mL
500 mg	10 mL	5 mL
750 mg	15 mL	7.5 mL

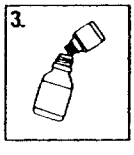
Preparation of the suspension:



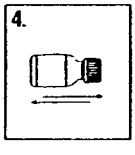
1. The small bottle contains the microcapsules, the large bottle contains the diluent.



2. Open both bottles. Child-proof cap: Press down according to instructions on the cap while turning to the left.



3. Pour the microcapsules completely into the larger bottle of diluent. **Do not add water to the suspension.**



4. Remove the top layer of the diluent bottle label (to reveal the CIPRO Oral Suspension label). Close the large bottle completely according to the directions on the cap and shake vigorously for about 15 seconds. The suspension is ready for use.

CIPRO Oral Suspension should not be administered through feeding tubes due to its physical characteristics.

Instruct the patient to shake CIPRO Oral Suspension vigorously each time before use for approximately 15 seconds and not to chew the microcapsules.

References:

1 National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol 20, No 2, NCCLS, Wayne, PA, January, 2000. 2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests-Seventh Edition Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1, NCCLS, Wayne, PA, January 2000 3. Report presented at the FDA's Anti-Infective Drug and Dermatological Drug Product's Advisory Committee meeting March 31, 1993, Silver Spring, MD. Report available from FDA, CDER, Advisors and Consultants Staff, HFD-21, 1901 Chapman Avenue, Room 200, Rockville, MD 20852, USA. 4. 21 CFR 314.510 (Subpart H – Accelerated Approval of New Drugs for Life-Threatening Illnesses). 5. Kelly DJ, et al Serum concentrations of penicillin, doxycycline, and ciprofloxacin during prolonged therapy in rhesus monkeys J Infect Dis 1992; 166 1184-7 6. Friedlander AM, et al Postexposure prophylaxis against experimental inhalational anthrax. J Infect Dis 1993; 167.1239-42. 7. Friedman J, Polifka J. Teratogenic effects of drugs: a resource for clinicians (TERIS) Baltimore, Maryland Johns Hopkins University Press, 2000 149-195 8. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones a multicenter prospective controlled study Antimicrob Agents Chemother 1998,42(6) 1336-1339 9. Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European network of teratology information services (ENTIS) Eur J Obstet Gynecol Reprod Biol. 1996 69 83-89

Patient Information About:

CIPRO®

(ciprofloxacin hydrochloride) TABLETS

CIPRO®

(ciprofloxacin*) ORAL SUSPENSION

This section contains important patient information about CIPRO (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin*) Oral Suspension and should be read completely before you begin treatment. This section does not take the place of discussion with your doctor or health care professional about your medical condition or your treatment. This section does not list all benefits and risks of CIPRO. If you have any concerns about your condition or your medicine, ask your doctor. Only your doctor can determine if CIPRO is right for you.

What is CIPRO?

CIPRO is an antibiotic used to treat bladder, kidney, prostate, cervix, stomach, intestine, lung, sinus, bone, and skin infections caused by certain germs called bacteria. CIPRO kills many types of bacteria that can infect these areas of the body. CIPRO has been shown in a large number of clinical trials to be safe and effective for the treatment of bacterial infections.

Sometimes viruses rather than bacteria may infect the lungs and sinuses (for example the common cold). CIPRO, like all other antibiotics, does not kill viruses. You should contact your doctor if your condition is not improving while taking CIPRO.

CIPRO Tablets are white to slightly yellow in color and are available in 100 mg, 250 mg, 500 mg and 750 mg strengths. CIPRO Oral Suspension is white to slightly yellow in color and is available in concentrations of 250 mg per teaspoon (5%) and 500 mg per teaspoon (10%).

How and when should I take CIPRO?

CIPRO Tablets:

Unless directed otherwise by your physician, CIPRO should be taken twice a day at approximately the same time, in the morning and in the evening. CIPRO can be taken with food or on an empty stomach. CIPRO should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone; however, CIPRO may be taken with a meal that contains these products.

You should take CIPRO for as long as your doctor prescribes it, even after you start to feel better. Stopping an antibiotic too early may result in failure to cure your infection. Do not take a double dose of CIPRO even if you miss a dose by mistake.

CIPRO Oral Suspension:

Take CIPRO Oral Suspension in the same way as above. In addition, remember to **shake the bottle vigorously each time before use for approximately 15 seconds** to make sure the suspension is mixed well. Be sure to swallow the required amount of suspension. Do not chew the microcapsules. Close the bottle completely after use. The product can be used for 14 days when stored in a refrigerator or at room temperature. After treatment has been completed, any remaining suspension should be discarded.

Who should not take CIPRO?

You should not take CIPRO if you have ever had a severe reaction to any of the group of antibiotics known as "quinolones."

CIPRO is not recommended during pregnancy or nursing, as the effects of CIPRO on the unborn child or nursing infant are unknown. If you are pregnant or plan to become pregnant while taking CIPRO talk to your doctor before taking this medication.

In general, CIPRO is not recommended for persons less than 18 years of age.

What are the possible side effects of CIPRO?

CIPRO is generally well tolerated. The most common side effects, which are usually mild, include nausea, diarrhea, vomiting, and abdominal pain/discomfort. If diarrhea persists, call your health care professional.

Rare cases of allergic reactions have been reported in patients receiving quinolones, including CIPRO, even after just one dose. If you develop hives, difficulty breathing, or other symptoms of a severe allergic reaction, seek emergency treatment right away. If you develop a skin rash, you should stop taking CIPRO and call your health care professional.

Some patients taking quinolone antibiotics may become more sensitive to sunlight or ultraviolet light such as that used in tanning salons. You should avoid excessive exposure to sunlight or ultraviolet light while you are taking CIPRO.

You should be careful about driving or operating machinery until you are sure CIPRO is not causing dizziness. Convulsions have been reported in patients receiving quinolone antibiotics including ciprofloxacin. Be sure to let your physician know if you have a history of convulsions. Quinolones, including ciprofloxacin, have been rarely associated with other central nervous system events including confusion, tremors, hallucinations, and depression.

CIPRO has been rarely associated with inflammation of tendons. If you experience pain, swelling or rupture of a tendon, you should stop taking CIPRO and call your health care professional.

If you notice any side effects not mentioned in this section, or if you have any concerns about side effects you may be experiencing, please inform your health care professional.

What about other medications I am taking?

CIPRO can affect how other medicines work. Tell your doctor about all other prescription and non-prescription medicines or supplements you are taking. This is especially important if you are taking theophylline. Other medications including warfarin, glyburide, and phenytoin may also interact with CIPRO.

Many antacids, multivitamins, and other dietary supplements containing magnesium, calcium, aluminum, iron or zinc can interfere with the absorption of CIPRO and may prevent it from working. Other medications such as sucralfate and Videx® (didanosine) chewable/buffered tablets or pediatric powder may also stop CIPRO from working. You should take CIPRO either 2 hours before or 6 hours after taking these products.

What if I have been prescribed CIPRO for possible anthrax exposure?

CIPRO has been approved to reduce the chance of developing anthrax infection following exposure to the anthrax bacteria. In general, CIPRO is not recommended for children, however, it is approved for use in patients younger than 18 years old for anthrax exposure. If you are pregnant, or plan to become pregnant while taking CIPRO, you and your doctor should discuss if the benefits of taking CIPRO for anthrax outweigh the risks.

CIPRO is generally well tolerated. Side effects that may occur during treatment to prevent anthrax might be acceptable due to the seriousness of the disease. You and your doctor should discuss the risks of not taking your medicine against the risks of experiencing side effects.

CIPRO can cause dizziness, confusion, or other similar side effects in some people. Therefore, it is important to know how CIPRO affects you before driving a car or performing other activities that require you to be alert and coordinated such as operating machinery.

Your doctor has prescribed CIPRO only for you. Do not give it to other people. Do not use it for a condition for which it was not prescribed. You should take your CIPRO for as long as your doctor prescribes it; stopping CIPRO too early may result in failure to prevent anthrax.

Remember:

Do not give CIPRO to anyone other than the person for whom it was prescribed.

Take your dose of CIPRO in the morning and in the evening.

Complete the course of CIPRO even if you are feeling better.

Keep CIPRO and all medications out of reach of children.

* Does not comply with USP with regards to "loss on drying" and "residue on ignition"

Bayer HealthCare

Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06516

Rx Only

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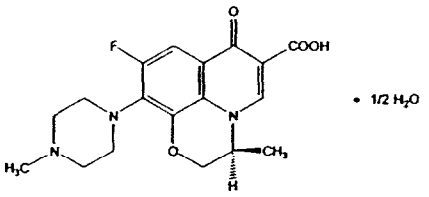
CIPRO (ciprofloxacin*) 5% and 10% Oral Suspension Made in Italy

Printed in U.S.A.

LEVAQUIN® (levofloxacin) Tablets
LEVAQUIN® (levofloxacin) Injection
LEVAQUIN® (levofloxacin in 5% dextrose) Injection

DESCRIPTION

LEVAQUIN® (levofloxacin) is a synthetic broad spectrum antibacterial agent for oral and intravenous administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate.

The chemical structure is: 

Its empirical formula is $C_{18}H_{20}FN_3O_4 \bullet \frac{1}{2} H_2O$ and its molecular weight is 370.38. Levofloxacin is a light yellowish-white to yellow-white crystal or crystalline powder. The molecule exists as a zwitterion at the pH conditions in the small intestine.

The data demonstrate that from pH 0.6 to 5.8, the solubility of levofloxacin is essentially constant (approximately 100 mg/mL). Levofloxacin is considered *soluble to freely soluble* in this pH range, as defined by USP nomenclature. Above pH 5.8, the solubility increases rapidly to its maximum at pH 6.7 (272 mg/mL) and is considered *freely soluble* in this range. Above pH 6.7, the solubility decreases and reaches a minimum value (about 50 mg/mL) at a pH of approximately 6.9.

Levofloxacin has the potential to form stable coordination compounds with many metal ions. This in vitro chelation potential has the following formation order: $Al^{+3} > Cu^{+2} > Zn^{+2} > Mg^{+2} > Ca^{+2}$.

LEVAQUIN Tablets are available as film-coated tablets and contain the following inactive ingredients:

250 mg (as expressed in the anhydrous form): hydroxypropyl methylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80 and synthetic red iron oxide.

500 mg (as expressed in the anhydrous form): hydroxypropyl methylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80 and synthetic red and yellow iron oxides.

750 mg (as expressed in the anhydrous form): hydroxypropyl methylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide,

polysorbate 80.

LEVAQUIN Injection in Single-Use Vials is a sterile, preservative-free aqueous solution of levofloxacin with pH ranging from 3.8 to 5.8. LEVAQUIN Injection in Premix Flexible Containers is a sterile, preservative-free aqueous solution of levofloxacin with pH ranging from 3.8 to 5.8. The appearance of LEVAQUIN Injection may range from a clear yellow to a greenish-yellow solution. This does not adversely affect product potency.

LEVAQUIN Injection in Single-Use Vials contains levofloxacin in Water for Injection. LEVAQUIN Injection in Premix Flexible Containers is a dilute, non-pyrogenic, nearly isotonic premixed solution that contains levofloxacin in 5% Dextrose (D_5W). Solutions of hydrochloric acid and sodium hydroxide may have been added to adjust the pH.

The flexible container is fabricated from a specially formulated non-plasticized, thermoplastic copolyester (CR3). The amount of water that can permeate from the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the flexible container can leach out certain of the container's chemical components in very small amounts within the expiration period. The suitability of the container material has been confirmed by tests in animals according to USP biological tests for plastic containers.

CLINICAL PHARMACOLOGY

The mean ±SD pharmacokinetic parameters of levofloxacin determined under single and steady state conditions following oral (p.o.) or intravenous (i.v.) doses of levofloxacin are summarized in Table 1.

Absorption

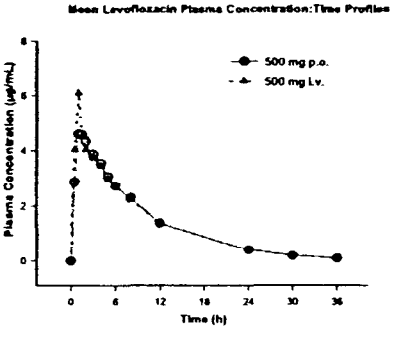
Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The absolute bioavailability of a 500 mg tablet and a 750 mg tablet of levofloxacin are both approximately 99%, demonstrating complete oral absorption of levofloxacin. Following a single intravenous dose of levofloxacin to healthy volunteers, the mean ±SD peak plasma concentration attained was 6.2 ±1.0 µg/mL after a 500 mg dose infused over 60 minutes and 11.5 ±4.0 µg/mL after a 750 mg dose infused over 90 minutes.

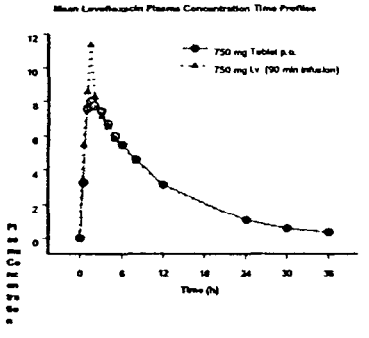
Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral /or i.v. dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosage regimen. The mean ±SD peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately 5.7 ±1.4 and 0.5 ±0.2 µg/mL after the 500 mg doses, and 8.6 ±1.9 and 1.1 ±0.4 µg/mL after the 750 mg doses, respectively. The mean ±SD peak and trough plasma concentrations attained following multiple

once-daily i.v. regimens were approximately 6.4 ±0.8 and 0.6 ±0.2 µg/mL after the 500 mg doses, and 12.1 ±4.1 and 1.3 ±0.71 µg/mL after the 750 mg doses, respectively.

Oral administration of a 500-mg LEVAQUIN tablet with food slightly prolongs the time to peak concentration by approximately 1 hour and slightly decreases the peak concentration by approximately 14%. Therefore, levofloxacin tablets can be administered without regard to food.

The plasma concentration profile of levofloxacin after i.v. administration is similar and comparable in extent of exposure (AUC) to that observed for levofloxacin tablets when equal doses (mg/mg) are administered. Therefore, the oral and i.v. routes of administration can be considered interchangeable. (See following chart.)





Distribution

The mean volume of distribution of levofloxacin generally ranges from 74 to 112 L after single and multiple 500 mg or 750 mg doses, indicating widespread distribution into body tissues. Levofloxacin reaches its peak levels in skin tissues and in blister fluid of healthy subjects at approximately 3 hours after dosing. The skin tissue biopsy to plasma AUC ratio is approximately 2 and the blister fluid to plasma AUC ratio is approximately 1 following multiple once-daily oral administration of 750 mg and 500 mg levofloxacin, respectively, to healthy subjects. Levofloxacin also penetrates well into lung tissues. Lung tissue concentrations were generally 2- to 5- fold higher than plasma concentrations and ranged from approximately 2.4 to 11.3 µg/g

over a 24-hour period after a single 500 mg oral dose.

In vitro, over a clinically relevant range (1 to 10 μg/mL) of serum/plasma levofloxacin concentrations, levofloxacin is approximately 24 to 38% bound to serum proteins across all species studied, as determined by the equilibrium dialysis method. Levofloxacin is mainly bound to serum albumin in humans. Levofloxacin binding to serum proteins is independent of the drug concentration.

Metabolism

Levofloxacin is stereochemically stable in plasma and urine and does not invert metabolically to its enantiomer, D-ofloxacin. Levofloxacin undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. Following oral administration, approximately 87% of an administered dose was recovered as unchanged drug in urine within 48 hours, whereas less than 4% of the dose was recovered in feces in 72 hours. Less than 5% of an administered dose was recovered in the urine as the desmethyl and N-oxide metabolites, the only metabolites identified in humans. These metabolites have little relevant pharmacological activity.

Excretion

Levofloxacin is excreted largely as unchanged drug in the urine. The mean terminal plasma elimination half-life of levofloxacin ranges from approximately 6 to 8 hours following single or multiple doses of levofloxacin given orally or intravenously. The mean apparent total body clearance and renal clearance range from approximately 144 to 226 mL/min and 96 to 142 mL/min, respectively. Renal clearance in excess of the glomerular filtration rate suggests that tubular secretion of levofloxacin occurs in addition to its glomerular filtration. Concomitant administration of either cimetidine or probenecid results in approximately 24% and 35% reduction in the levofloxacin renal clearance, respectively, indicating that secretion of levofloxacin occurs in the renal proximal tubule. No levofloxacin crystals were found in any of the urine samples freshly collected from subjects receiving levofloxacin.

Special Populations

Geriatric: There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects when the subjects' differences in creatinine clearance are taken into consideration. Following a 500 mg oral dose of levofloxacin to healthy elderly subjects (66 - 80 years of age), the mean terminal plasma elimination half-life of levofloxacin was about 7.6 hours, as compared to approximately 6 hours in younger adults. The difference was attributable to the variation in renal function status of the subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by age. Levofloxacin dose adjustment based on age alone is not necessary.

Pediatric: The pharmacokinetics of levofloxacin in pediatric subjects have not been studied.

Gender: There are no significant differences in levofloxacin pharmacokinetics between male and female subjects when subjects' differences in creatinine clearance are taken into consideration. Following a 500 mg oral dose of levofloxacin to healthy male subjects, the mean terminal plasma elimination half-life of levofloxacin was about 7.5 hours, as compared to approximately 6.1 hours in female subjects. This difference was attributable to the variation in renal function status of the male and female subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by the gender of the subjects. Dose adjustment based on gender alone is not necessary.

Race: The effect of race on levofloxacin pharmacokinetics was examined through a covariate analysis performed on data from 72 subjects: 48 white and 24 nonwhite. The apparent total body clearance and apparent volume of distribution were not affected by the race of the subjects.

Renal insufficiency: Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance <50mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating that supplemental doses of levofloxacin are not required following hemodialysis or CAPD. (See **PRECAUTIONS: General** and **DOSAGE AND ADMINISTRATION**.)

Hepatic insufficiency: Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

Bacterial infection: The pharmacokinetics of levofloxacin in patients with serious community-acquired bacterial infections are comparable to those observed in healthy subjects.

Drug-drug interactions: The potential for pharmacokinetic drug interactions between levofloxacin and theophylline, warfarin, cyclosporine, digoxin, probenecid, cimetidine, sucralfate, and antacids has been evaluated. (See **PRECAUTIONS: Drug Interactions**.)

Table 1. Mean ±SD Levofloxacin PK Parameters

Regimen	C_{max} (μg/mL)	T_{max} (h)	AUC (μg•h/mL)	CL/F[1] (mL/min)	Vd/F[2] (L)	$t_{1/2}$ (h)	CL_R (mL/min)
Single dose							
250 mg p.o.[3]	2.8 ± 0.4	1.6 ± 1.0	27.2 ± 3.9	156 ± 20	ND	7.3 ± 0.9	142 ± 21
500 mg p.o.[3*]	5.1 ± 0.8	1.3 ± 0.6	47.9 ± 6.8	178 ± 28	ND	6.3 ± 0.6	103 ± 30
500 mg i.v.[3]	6.2 ± 1.0	1.0 ± 0.1	48.3 ± 5.4	175 ± 20	90 ± 11	6.4 ± 0.7	112 ± 25
750 mg p.o.[5*]	9.3 ± 1.6	1.6 ± 0.8	101 ± 20	129 ± 24	83 ± 17	7.5 ± 0.9	ND
750 mg i.v.[5]	11.5 ±4.0	ND	110 ±40	126 ±39	75 ± 13	7.5 ± 1.6	ND
Multiple dose							
500 mg q24h p.o.[3]	5.7 ± 1.4	1.1 ± 0.4	47.5 ± 6.7	175 ± 25	102 ± 22	7.6 ± 1.6	116 ± 31
500 mg q24h i.v.[3]	6.4 ± 0.8	ND	54.6 ± 11.1	158 ± 29	91 ± 12	7.0 ± 0.8	99 ± 28
500 mg or 250 mg q24h i.v., patients with bacterial infection[6]	8.7± 4.0[7]	ND	72.5 ± 51.2[7]	154 ± 72	111 ± 58	ND	ND
750 mg q24h p.o.[5]	8.6 ± 1.9	1.4 ± 0.5	90.7 ± 17.6	143 ± 29	100 ± 16	8.8 ± 1.5	116 ± 28
750 mg q24h i.v.[5]	12.1 ± 4.1[4]	ND	108 ± 34	126 ± 37	80 ± 27	7.9 ± 1.9	ND
500 mg p.o. single dose, effects of gender and age:							
Male[8]	5.5 ± 1.1	1.2 ± 0.4	54.4 ± 18.9	166 ± 44	89 ± 13	7.5 ± 2.1	126 ± 38
Female[9]	7.0 ± 1.6	1.7 ± 0.5	67.7 ± 24.2	136 ± 44	62 ± 16	6.1 ± 0.8	106 ± 40
Young[10]	5.5 ± 1.0	1.5 ± 0.6	47.5 ± 9.8	182 ± 35	83 ± 18	6.0 ± 0.9	140 ± 33
Elderly[11]	7.0 ± 1.6	1.4 ± 0.5	74.7 ± 23.3	121 ± 33	67 ± 19	7.6 ± 2.0	91 ± 29
500 mg p.o. single dose, patients with renal insufficiency:							
CL_{CR} 50-80 mL/min	7.5 ± 1.8	1.5 ± 0.5	95.6 ± 11.8	88 ± 10	ND	9.1 ± 0.9	57 ± 8
CL_{CR} 20-49 mL/min	7.1 ± 3.1	2.1 ± 1.3	182.1 ± 62.6	51 ± 19	ND	27 ± 10	26 ± 13
CL_{CR} <20 mL/min	8.2 ± 2.6	1.1 ± 1.0	263.5 ± 72.5	33 ± 8	ND	35 ± 5	13 ± 3
Hemodialysis	5.7 ± 1.0	2.8 ± 2.2	ND	ND	ND	76 ± 42	ND
CAPD	6.9 ± 2.3	1.4 ± 1.1	ND	ND	ND	51 ± 24	ND

[1] clearance/bioavailability

[2] volume of distribution/bioavailability

[3] healthy males 18-53 years of age

[4] 60 min infusion for 250 mg and 500 mg doses, 90 min infusion for 750 mg dose

[5] healthy male and female subjects 18-54 years of age

[6] 500 mg q48h for patients with moderate renal impairment (CL_{CR} 20-50 mL/min) and infections of the respiratory tract or skin

[7] dose-normalized values (to 500 mg dose), estimated by population pharmacokinetic modeling

[8] healthy males 22-75 years of age

[9] healthy females 18-80 years of age

[10] young healthy male and female subjects 18-36 years of age

[11] healthy elderly male and female subjects 66-80 years of age

*Absolute bioavailability; F = 0.99 ± 0.08 from a 500-mg tablet and F = 0.99 ± 0.06 from a 750-mg tablet ; ND = not determined.

MICROBIOLOGY

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Levofloxacin has in vitro activity against a wide range of gram-negative and gram-positive microorganisms. Levofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and β-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Resistance to levofloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10^{-9} to 10^{-10}). Although cross-resistance has been observed between levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to levofloxacin.

Levofloxacin has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-positive microorganisms

Enterococcus faecalis (many strains are only moderately susceptible)

Staphylococcus aureus (methicillin-susceptible strains)

Staphylococcus epidermidis (methicillin-susceptible strains)

Staphylococcus saprophyticus

Streptococcus pneumoniae (including penicillin-resistant strains*)

Streptococcus pyogenes

*Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC value of — 2 μg/mL

Aerobic gram-negative microorganisms

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae

Legionella pneumophila

Moraxella catarrhalis

Proteus mirabilis

Pseudomonas aeruginosa

Serratia marcescens

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin.

Other microorganisms

Chlamydia pneumoniae

Mycoplasma pneumoniae

The following in vitro data are available, **but their clinical significance is unknown.**

Levofloxacin exhibits in vitro minimum inhibitory concentrations (MIC values) of 2 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of levofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic gram-positive microorganisms

Staphylococcus haemolyticus

Streptococcus (Group C/F)

Streptococcus (Group G)

Streptococcus agalactiae

Streptococcus milleri

Viridans group streptococci

Aerobic gram-negative microorganisms

Acinetobacter baumannii

Acinetobacter lwoffii

Bordetella pertussis

Citrobacter (diversus) koseri

Citrobacter freundii

Enterobacter aerogenes

Enterobacter sakazakii

Klebsiella oxytoca

Morganella morganii

Pantoea (Enterobacter) agglomerans

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Pseudomonas fluorescens

Anaerobic gram-positive microorganisms

Clostridium perfringens

Susceptibility Tests

Susceptibility testing for levofloxacin should be performed, as it is the optimal predictor of activity.

Dilution techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC values). These MIC values provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a

standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of levofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae,* Enterococci, *Staphylococcus* species, and *Pseudomonas aeruginosa:*

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae:*[a]

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)

[a] These interpretive standards are applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.[1]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* spp. including *S. pneumoniae*:[b]

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the

antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard levofloxacin powder should give the following MIC values:

Microorganism		MIC (µg/mL)
Enterococcus faecalis	ATCC 29212	0.25 – 2
Escherichia coli	ATCC 25922	0.008 - 0.06
Escherichia coli	ATCC 35218	0.015 - 0.06
Haemophilus influenzae	ATCC 49247[c]	0.008 - 0.03
Pseudomonas aeruginosa	ATCC 27853	0.5 – 4
Staphylococcus aureus	ATCC 29213	0.06 - 0.5
Streptococcus pneumoniae	ATCC 49619[d]	0.5 – 2

[c] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using Haemophilus Test Medium (HTM).[1]

[d] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg levofloxacin to test the susceptibility of microorganisms to levofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg levofloxacin disk should be interpreted according to the following criteria:

For testing *Enterobacteriaceae,* Enterococci, *Staphylococcus* species, and *Pseudomonas aeruginosa:*

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)
14-16	Intermediate (I)
≤13	Resistant (R)

For *Haemophilus influenzae* and *Haemophilus parainfluenzae:*[e]

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)

[e] These interpretive standards are applicable only to disk diffusion susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding zone diameter results suggestive of a "nonsusceptible" category

should be submitted to a reference laboratory for further testing.

For *Streptococcus* spp. including *S. pneumoniae*:[f]

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)
14-16	Intermediate (I)
≤13	Resistant (R)

[f] These zone diameter standards for *Streptococcus* spp. including *S. pneumoniae* apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for levofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-μg levofloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	29 - 37
Haemophilus influenzae	ATCC 49247[g]	32 - 40
Pseudomonas aeruginosa	ATCC 27853	19 - 26
Staphylococcus aureus	ATCC 25923	25 - 30
Streptococcus pneumoniae	ATCC 49619[h]	20 - 25

[g] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using Haemophilus Test Medium (HTM).[2]

[h] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

INDICATIONS AND USAGE

LEVAQUIN Tablets/Injection are indicated for the treatment of adults (≥18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below. LEVAQUIN Injection is indicated when intravenous administration offers a route of administration advantageous to the patient (e.g., patient cannot tolerate an oral dosage form). Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Acute maxillary sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.

Acute bacterial exacerbation of chronic bronchitis due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Moraxella*

catarrhalis.

Nosocomial pneumonia due to methicillin-susceptible *Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae,* or *Streptococcus pneumoniae.* Adjunctive therapy should be used as clinically indicated. Where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended. (See **CLINICAL STUDIES.)**

Community-acquired pneumonia due to *Staphylococcus aureus, Streptococcus pneumoniae* (including penicillin-resistant strains, MIC value for penicillin —2 μg/mL), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila,* or *Mycoplasma pneumoniae.* (See **CLINICAL STUDIES.)**

Complicated skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes, or Proteus mirabilis.*

Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to *Staphylococcus aureus,* or *Streptococcus pyogenes.*

Chronic bacterial prostatitis due to *Escherichia coli, Enterococcus faecalis,* or *Staphylococcus epidermidis.*

Complicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* or *Pseudomonas aeruginosa.*

Acute pyelonephritis (mild to moderate) caused by *Escherichia coli.*

Uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli, Klebsiella pneumoniae,* or *Staphylococcus saprophyticus.*

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to levofloxacin. Therapy with levofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be selected.

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin. Culture and susceptibility testing

performed periodically during therapy will provide information about the continued susceptibility of the pathogens to the antimicrobial agent and also the possible emergence of bacterial resistance.

CONTRAINDICATIONS

Levofloxacin is contraindicated in persons with a history of hypersensitivity to levofloxacin, quinolone antimicrobial agents, or any other components of this product.

WARNINGS

THE SAFETY AND EFFICACY OF LEVOFLOXACIN IN PEDIATRIC PATIENTS, ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pediatric Use, Pregnancy,** and **Nursing Mothers** subsections.)

In immature rats and dogs, the oral and intravenous administration of levofloxacin increased the incidence and severity of osteochondrosis. Other fluoroquinolones also produce similar erosions in the weight bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY**.)

Convulsions and toxic psychoses have been reported in patients receiving quinolones, including levofloxacin. Quinolones may also cause increased intracranial pressure and central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving levofloxacin, the drug should be discontinued and appropriate measures instituted. As with other quinolones, levofloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction.) (See **PRECAUTIONS: General, Information for Patients, Drug Interactions** and **ADVERSE REACTIONS.)**

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including levofloxacin. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching,

and other serious skin reactions. Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. (See **PRECAUTIONS** and **ADVERSE REACTIONS**.)

Serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including levofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis; arthralgia; myalgia; serum sickness; allergic pneumonitis; interstitial nephritis; acute renal insufficiency or failure; hepatitis; jaundice; acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity and supportive measures instituted. (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS**.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including levofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. (See **ADVERSE REACTIONS**.)

Ruptures of the shoulder, hand, or Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including levofloxacin. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially in the elderly. Levofloxacin should

be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones, including levofloxacin.

PRECAUTIONS

General

Because a rapid or bolus intravenous injection may result in hypotension, LEVOFLOXACIN INJECTION SHOULD ONLY BE ADMINISTERED BY SLOW INTRAVENOUS INFUSION OVER A PERIOD OF 60 OR 90 MINUTES DEPENDING ON THE DOSAGE. (See **DOSAGE AND ADMINISTRATION.**)

Although levofloxacin is more soluble than other quinolones, adequate hydration of patients receiving levofloxacin should be maintained to prevent the formation of a highly concentrated urine.

Administer levofloxacin with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of levofloxacin may be reduced. In patients with impaired renal function (creatinine clearance <50 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION.**)

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving drugs in this class. Excessive exposure to sunlight should be avoided. However, in clinical trials with levofloxacin, phototoxicity has been observed in less than 0.1% of patients. Therapy should be discontinued if phototoxicity (e.g., a skin eruption) occurs.

As with other quinolones, levofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). (See **WARNINGS** and **Drug Interactions**.)

As with other quinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide/glibenclamide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with levofloxacin, levofloxacin should be discontinued

immediately and appropriate therapy should be initiated immediately. (See **Drug Interactions** and **ADVERSE REACTIONS.**)

Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. During post-marketing surveillance, rare cases of torsades de pointes have been reported in patients taking levofloxacin. These reports generally involved patients with concurrent medical conditions or concomitant medications that may have been contributory. The risk of arrhythmias may be reduced by avoiding concurrent use with other drugs that prolong the QT interval including class Ia or class III antiarrhythmic agents; in addition, use of levofloxacin in the presence of risk factors for torsades de pointes such as hypokalemia, significant bradycardia, and cardiomyopathy should be avoided.

As with any potent antimicrobial drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during therapy. (See **WARNINGS** and **ADVERSE REACTIONS.**)

Information for Patients

Patients should be advised:

- to drink fluids liberally;
- that antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or Videx® (didanosine), chewable/buffered tablets or the pediatric powder for oral solution should be taken at least two hours before or two hours after oral levofloxacin administration. (See **Drug Interactions**);
- that oral levofloxacin can be taken without regard to meals;
- that levofloxacin may cause neurologic adverse effects (e.g., dizziness, lightheadedness) and that patients should know how they react to levofloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. (See **WARNINGS** and **ADVERSE REACTIONS**);
- to discontinue treatment and inform their physician if they experience pain, inflammation, or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded;
- that levofloxacin may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling

suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction. (See **WARNINGS** and **ADVERSE REACTIONS**);

- to avoid excessive sunlight or artificial ultraviolet light while receiving levofloxacin and to discontinue therapy if phototoxicity (i.e., skin eruption) occurs;
- that if they are diabetic and are being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, they should discontinue levofloxacin and consult a physician. (See **PRECAUTIONS: General** and **Drug Interactions.**);
- that concurrent administration of warfarin and levofloxacin has been associated with increases of the International Normalized Ratio (INR) or prothrombin time and clinical episodes of bleeding. Patients should notify their physician if they are taking warfarin.
- that convulsions have been reported in patients taking quinolones, including levofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

Drug Interactions

Antacids, Sucralfate, Metal Cations, Multivitamins

LEVAQUIN Tablets: While the chelation by divalent cations is less marked than with other quinolones, concurrent administration of LEVAQUIN Tablets with antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc may interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. Tablets with antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamins preparations with zinc or Videx® (didanosine), chewable/buffered tablets or the pediatric powder for oral solution may substantially interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. These agents should be taken at least two hours before or two hours after levofloxacin administration.

LEVAQUIN Injection: There are no data concerning an interaction of **intravenous** quinolones with **oral** antacids, sucralfate, multivitamins, Videx® (didanosine), or metal cations. However, no quinolone should be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line. (See **DOSAGE AND ADMINISTRATION.**)

Theophylline: No significant effect of levofloxacin on the plasma concentrations, AUC, and other disposition parameters for theophylline was detected in a clinical study involving 14 healthy volunteers. Similarly, no apparent effect of theophylline on levofloxacin absorption and

disposition was observed. However, concomitant administration of other quinolones with theophylline has resulted in prolonged elimination half-life, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline-related adverse reactions in the patient population. Therefore, theophylline levels should be closely monitored and appropriate dosage adjustments made when levofloxacin is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels. (See **WARNINGS** and **PRECAUTIONS: General.**)

Warfarin: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for R- and S- warfarin was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of warfarin on levofloxacin absorption and disposition was observed. There have been reports during the post-marketing experience in patients that levofloxacin enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and levofloxacin use have been associated with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if levofloxacin is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding.

Cyclosporine: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for cyclosporine was detected in a clinical study involving healthy volunteers. However, elevated serum levels of cyclosporine have been reported in the patient population when co-administered with some other quinolones. Levofloxacin C_{max} and k_e were slightly lower while T_{max} and $t_{½}$ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

Digoxin: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for digoxin was detected in a clinical study involving healthy volunteers. Levofloxacin absorption and disposition kinetics were similar in the presence or absence of digoxin. Therefore, no dosage adjustment for levofloxacin or digoxin is required when administered concomitantly.

Probenecid and Cimetidine: No significant effect of probenecid or cimetidine on the rate and extent of levofloxacin absorption was observed in a clinical study involving healthy volunteers. The AUC and $t_{½}$ of levofloxacin were 27-38% and 30% higher, respectively, while CL/F and CL_R were 21-35% lower during concomitant treatment with probenecid or cimetidine compared to levofloxacin alone. Although these differences were statistically significant, the changes were not high enough to warrant dosage adjustment for levofloxacin when probenecid or

cimetidine is co-administered.

Non-steroidal anti-inflammatory drugs: The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures. (See **WARNINGS** and **PRECAUTIONS: General**.)

Antidiabetic agents: Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a lifetime bioassay in rats, levofloxacin exhibited no carcinogenic potential following daily dietary administration for 2 years; the highest dose (100 mg/kg/day) was 1.4 times the highest recommended human dose (750 mg) based upon relative body surface area. Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh-1) mice at any levofloxacin dose level and was therefore not photo-carcinogenic under conditions of this study. Dermal levofloxacin concentrations in the hairless mice ranged from 25 to 42 μg/g at the highest levofloxacin dose level (300 mg/kg/day) used in the photo-carcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg of levofloxacin averaged approximately 11.8 μg/g at Cmax.

Levofloxacin was not mutagenic in the following assays; Ames bacterial mutation assay (*S. typhimurium* and *E. coli*), CHO/HGPRT forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the mouse sister chromatid exchange assay. It was positive in the in vitro chromosomal aberration (CHL cell line) and sister chromatid exchange (CHL/IU cell line) assays.

Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day, corresponding to 4.2 times the highest recommended human dose based upon relative body surface area and intravenous doses as high as 100 mg/kg/day, corresponding to 1.2 times the highest recommended human dose based upon relative body surface area.

Pregnancy: Teratogenic Effects. Pregnancy Category C.

Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day which corresponds to 9.4 times the highest recommended human dose based upon relative body surface area, or at intravenous doses as high as 160 mg/kg/day corresponding to 1.9 times the highest recommended human dose based upon relative body surface area. The oral dose of

810 mg/kg/day to rats caused decreased fetal body weight and increased fetal mortality. No teratogenicity was observed when rabbits were dosed orally as high as 50 mg/kg/day which corresponds to 1.1 times the highest recommended human dose based upon relative body surface area, or when dosed intravenously as high as 25 mg/kg/day, corresponding to 0.5 times the highest recommended human dose based upon relative body surface area.

There are, however, no adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS.**)

Nursing Mothers

Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from levofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients and adolescents below the age of 18 years have not been established. Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. (See **WARNINGS.**)

Geriatric Use

In phase 3 clinical trials, 1,190 levofloxacin-treated patients (25%) were ≥65 years of age. Of these, 675 patients (14%) were between the ages of 65 and 74 and 515 patients (11%) were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

The pharmacokinetic properties of levofloxacin in younger adults and elderly adults do not differ significantly when creatinine clearance is taken into consideration. However since the drug is known to be substantially excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

The incidence of drug-related adverse reactions in patients during Phase 3 clinical trials

conducted in North America was ~~6.2%~~ 6.3%. Among patients receiving levofloxacin therapy, ~~4.1%~~ 4.0% discontinued levofloxacin therapy due to adverse experiences. The overall incidence, type and distribution of adverse events was similar in patients receiving levofloxacin doses of 750 mg once daily compared to patients receiving doses from 250 mg once daily to 500 mg twice daily.

In clinical trials, the following events were considered likely to be drug-related in patients receiving levofloxacin:

nausea 1.3%, diarrhea 1.0%, vaginitis ~~0.7%~~ 0.8% insomnia 0.4%, abdominal pain ~~0.4%~~ 0.5%, flatulence 0.3%, pruritus 0.3%, dizziness 0.3%, dyspepsia 0.3%, rash 0.3%, genital moniliasis 0.2%, taste perversion 0.2%, vomiting 0.2%, injection site pain 0.2%, injection site reaction 0.2%, injection site inflammation 0.1%, constipation 0.1%, fungal infection 0.1%, genital pruritis 0.1%, headache 0.1%, moniliasis 0.1%, nervousness 0.1%, rash erythematous 0.1%, urticaria 0.1%, maculopapular rash 0.1%.

In clinical trials, the following events occurred in >3% of patients, regardless of drug relationship:

nausea 7.0%, headache 6.1%, diarrhea 5.7%, insomnia ~~4.5%~~ 4.3%, ~~injection site reaction 3.5%,~~ constipation 3.3%.

In clinical trials, the following events occurred in 1 to 3% of patients, regardless of drug relationship:

dizziness ~~2.6%~~ 2.5%, abdominal pain ~~2.5%~~ 2.6% dyspepsia 2.3%, vomiting ~~2.4%~~ 2.3%, vaginitis 1.8%, ~~injection site pain 1.7%,~~ flatulence 1.4%, pain 1.4%, pruritus 1.3%, sinusitis 1.3%, chest pain ~~1.2%~~ 1.1%, fatigue 1.3%, rash 1.4%, back pain 1.1%, ~~injection site inflammation 1.1%,~~ rhinitis ~~1.0%~~ 1.1%, ~~taste perversion 1.0%.~~ dyspnea 1.1%, pharyngitis 1.0%.

In clinical trials, the following events, of potential medical importance, occurred at a rate of 0.1% to 1.0%, regardless of drug relationship:

~~Autonomic Nervous System Disorders:~~	~~Postural hypotension~~
Body as a Whole General Disorders:	Asthenia, fever, malaise, rigors, substernal chest pain, syncope, enlarged abdomen, allergic reaction, ~~headache~~, hot flashes, edema, influenza-like symptoms, leg pain, multiple organ failure, condition aggravated, peripheral edema
Cardiovascular Disorders, General:	Cardiac failure, circulatory failure, hypertension, hypotension, postural hypotension

Central and Peripheral Nervous System Disorders:	Abnormal coordination, coma, convulsions (seizures), hyperkinesia, hypertonia, hypoesthesia, involuntary muscle contractions, paresthesia, paralysis, speech disorder, stupor, tremor, vertigo, encephalopathy, abnormal gait, leg cramps, intracranial hypertension, ataxia, migraine
Gastro-Intestinal System Disorders:	Dry mouth, dysphagia, gastroenteritis, G.I. hemorrhage, pancreatitis, pseudomembranous colitis, tongue edema, gastritis, gastroesophageal reflux, melena, esophagitis, stomatitis, intestinal obstruction
Hearing and Vestibular Disorders:	Earache, tinnitus
Heart Rate and Rhythm Disorders:	Arrhythmia, atrial fibrillation, bradycardia, cardiac arrest, palpitation, supraventricular tachycardia, ventricular tachycardia, tachycardia, heart block, ventricular fibrillation
Liver and Biliary System Disorders:	~~Elevated bilirubin,~~ Abnormal hepatic function, cholelithiasis, jaundice, hepatic failure, hepatic coma, bilirubinemia
Metabolic and Nutritional Disorders:	Hypomagnesemia, thirst, aggravated diabetes mellitus, dehydration, hyperglycemia, hyperkalemia, hypoglycemia, hypokalemia, gout, hypernatremia, hypophosphatemia, increased LDH, weight decrease, fluid overload, electrolyte abnormality
Musculo-Skeletal System Disorders:	Arthralgia, arthritis, arthrosis, pathological fracture, myalgia, osteomyelitis, synovitis, tendonitis, muscle weakness, rhabdomyolysis, skeletal pain
Myo, Endo, Pericardial and Valve Disorders:	Angina pectoris, myocardial infarction, coronary thrombosis
Neoplasms:	Carcinoma
Other Special Senses Disorders:	Parosmia, taste perversion
Platelet, Bleeding and Clotting Disorders:	Pulmonary embolism, hematoma, epistaxis, purpura, thrombocytopenia, abnormal platelets, embolism (blood clot)
Psychiatric Disorders:	Abnormal dreaming, agitation, anorexia, anxiety, confusion, depression, hallucination, nervousness, paranoia, sleep disorder, somnolence, aggressive reaction, delirium, emotional lability, impaired concentration, impotence, manic reaction, mental deficiency, withdrawal syndrome
Red Blood Cell Disorders:	Anemia
Reproductive Disorders:	Dysmenorrhea, leukorrhea, ejaculation failure
Resistance Mechanism Disorders:	Abscess, herpes simplex, bacterial infection, viral infection, moniliasis, otitis media, sepsis, fungal infection, genital moniliasis
Respiratory System Disorders:	Bronchitis, epistaxis, pharyngitis, ~~rhinitis,~~ upper respiratory tract infection, asthma, coughing, dyspnea, hemoptysis, hypoxia, pleural effusion, respiratory insufficiency, airway obstruction, ARDS, aspiration, bronchospasm, emphysema, pneumonia, pneumothorax, pulmonary collapse, pulmonary edema, respiratory depression, respiratory disorder
Skin and Appendages Disorders:	~~Rash,~~ Dry skin, genital pruritus, increased sweating, skin disorder, skin exfoliation, skin ulceration, urticaria, bullous eruption, erythematous rash, maculopapular rash, alopecia, eczema

Urinary System Disorders:	Urinary tract infection, abnormal renal function, acute renal failure, hematuria, face edema, dysuria, oliguria, urinary incontinence, urinary retention
Vascular (Extracardiac) Disorders.	Cerebrovascular disorder, phlebitis, purpura, thrombophlebitis (deep), flushing, gangrene
Vision Disorders:	Abnormal vision, conjunctivitis, diplopia, eye pain
White Cell and RES Disorders:	Granulocytopenia, leukocytosis, lymphadenopathy, WBC abnormal (not otherwise specified), leukopenia

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with other quinolones. The relationship of the drugs to these events is not presently established.

Crystalluria and cylindruria have been reported with other quinolones.

The following markedly abnormal laboratory values appeared in >2% of patients receiving levofloxacin. It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

Blood Chemistry: decreased glucose (2.2%)

Hematology: decreased lymphocytes (~~2.4%~~ 2.3%)

It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

Post-Marketing Adverse Reactions

Additional adverse events reported from worldwide post-marketing experience with levofloxacin include: allergic pneumonitis, anaphylactic shock, anaphylactoid reaction, dysphonia, abnormal EEG, encephalopathy, eosinophilia, erythema multiforme, hemolytic anemia, multi-system organ failure, increased International Normalized Ratio (INR)/prothrombin time, Stevens-Johnson Syndrome, tendon rupture, torsades de pointes, vasodilation.

OVERDOSAGE

Levofloxacin exhibits a low potential for acute toxicity. Mice, rats, dogs and monkeys exhibited the following clinical signs after receiving a single high dose of levofloxacin: ataxia, ptosis, decreased locomotor activity, dyspnea, prostration, tremors, and convulsions. Doses in excess of 1500 mg/kg orally and 250 mg/kg i.v. produced significant mortality in rodents. In the event of an acute overdosage, the stomach should be emptied. The patient should be observed and

appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

LEVAQUIN Injection should only be administered by intravenous infusion. It is not for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED. Levofloxacin Injection should be infused intravenously slowly over a period of not less than 60 or 90 minutes, depending on the dosage. (See **PRECAUTIONS.**)

Single-use vials require dilution prior to administration. (See **PREPARATION FOR ADMINISTRATION.**)

The usual dose of LEVAQUIN Tablets or Injection is 250 mg or 500 mg administered orally or by slow infusion over 60 minutes every 24 hours or 750 mg administered orally or by slow infusion over 90 minutes every 24 hours, as indicated by infection and described in the following dosing chart. These recommendations apply to patients with normal renal function (i.e., creatinine clearance > 80 mL/min). For patients with altered renal function see the **Patients with Impaired Renal Function** subsection. Oral doses should be administered at least two hours before or two hours after antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or Videx® (didanosine), chewable/buffered tablets or the pediatric powder for oral solution.

Patients with Normal Renal Function

Infection*	Unit Dose	Freq.	Duration**	Daily Dose
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	q24h	7 days	500 mg
Nosocomial Pneumonia	750 mg	q24h	7-14 days	750 mg
Comm. Acquired Pneumonia	500 mg	q24h	7-14 days	500 mg
Acute Maxillary Sinusitis	500 mg	q24h	10-14 days	500 mg
Complicated SSSI	750 mg	q24h	7-14 days	750 mg
Uncomplicated SSSI	500 mg	q24h	7-10 days	500 mg
Chronic Bacterial Prostatitis	500 mg	q24h	28 days	500 mg
Complicated UTI	250 mg	q24h	10 days	250 mg
Acute pyelonephritis	250 mg	q24h	10 days	250 mg
Uncomplicated UTI	250 mg	q24h	3 days	250 mg

* DUE TO THE DESIGNATED PATHOGENS (See INDICATIONS AND USAGE.)

** Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician.

Patients with Impaired Renal Function

Renal Status	Initial Dose	Subsequent Dose
Acute Bacterial Exacerbation of Chronic Bronchitis / Comm. Acquired Pneumonia / Acute Maxillary Sinusitis / Uncomplicated SSSI/Chronic Bacterial Prostatitis		
CL_{CR} from 50 to 80 mL/min	No dosage adjustment required	
CL_{CR} from 20 to 49 mL/min	500 mg	250 mg q24h
CL_{CR} from 10 to 19 mL/min	500 mg	250 mg q48h
Hemodialysis	500 mg	250 mg q48h
CAPD	500 mg	250 mg q48h
Complicated SSSI/Nosocomial Pneumonia		
CL_{CR} from 50 to 80 mL/min	No dosage adjustment required	
CL_{CR} from 20 to 49 mL/min	750 mg	750 mg q48h
CL_{CR} from 10 to 19 mL/min	750 mg	500 mg q48h
Hemodialysis	750 mg	500 mg q48h
CAPD	750 mg	500 mg q48h
Complicated UTI / Acute Pyelonephritis		
CL_{CR} ≥20 mL/min	No dosage adjustment required	
CL_{CR} from 10 to 19 mL/min	250 mg	250 mg q48h
Uncomplicated UTI	No dosage adjustment required	

CL_{CR}=creatinine clearances
CAPD=chronic ambulatory peritoneal dialysis

When only the serum creatinine is known, the following formula may be used to estimate creatinine clearance.

Men: Creatinine Clearance (mL/min) =

$$\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men.

The serum creatinine should represent a steady state of renal function.

Preparation of Levofloxacin Injection for Administration

LEVAQUIN Injection in Single-Use Vials: LEVAQUIN Injection is supplied in single-use vials containing a concentrated levofloxacin solution with the equivalent of 500 mg (20 mL vial) and 750 mg (30 mL vial) of levofloxacin in Water for Injection, USP. The 20 mL and 30 mL vials each contain 25 mg of levofloxacin/mL. **THESE LEVAQUIN INJECTION SINGLE-USE VIALS MUST BE FURTHER DILUTED WITH AN APPROPRIATE SOLUTION PRIOR TO INTRAVENOUS ADMINISTRATION.** (See **COMPATIBLE INTRAVENOUS SOLUTIONS.**) The concentration of the resulting diluted solution should be

5 mg/mL prior to administration.

This intravenous drug product should be inspected visually for particulate matter prior to administration. Samples containing visible particles should be discarded.

Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final intravenous solution. **Since the vials are for single-use only, any unused portion remaining in the vial should be discarded. When used to prepare two 250 mg doses from the 20 mL vial containing 500 mg of levofloxacin, the full content of the vial should be withdrawn at once using a single-entry procedure, and a second dose should be prepared and stored for subsequent use.** (See **Stability of LEVAQUIN Injection Following Dilution.**)

Since only limited data are available on the compatibility of levofloxacin intravenous injection with other intravenous substances, **additives or other medications should not be added to LEVAQUIN Injection in single-use vials or infused simultaneously through the same intravenous line.** If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of LEVAQUIN Injection with an infusion solution compatible with LEVAQUIN Injection and with any other drug(s) administered via this common line.

Prepare the desired dosage of levofloxacin according to the following chart:

Desired Dosage Strength	From Appropriate Vial, Withdraw Volume	Volume of Diluent	Infusion Time
250 mg	10 mL (20 mL Vial)	40 mL	60 min
500 mg	20 mL (20 mL Vial)	80 mL	60 min
750 mg	30 mL (30 mL Vial)	120 mL	90 min

For example, to prepare a 500 mg dose using the 20 mL vial (25 mg/mL), withdraw 20 mL and dilute with a compatible intravenous solution to a total volume of 100 mL.

Compatible Intravenous Solutions: Any of the following intravenous solutions may be used to prepare a 5 mg/mL levofloxacin solution with the approximate pH values:

Intravenous Fluids	Final pH of LEVAQUIN Solution

0.9% Sodium Chloride Injection, USP	4.71
5% Dextrose Injection, USP	4.58
5% Dextrose/0.9% NaCl Injection	4.62
5% Dextrose in Lactated Ringers	4.92
Plasma-Lyte® 56/5% Dextrose Injection	5.03
5% Dextrose, 0.45% Sodium Chloride, and 0.15% Potassium Chloride Injection	4.61
Sodium Lactate Injection (M/6)	5.54

LEVAQUIN Injection Premix in Single-Use Flexible Containers: LEVAQUIN Injection is also supplied in flexible containers containing a premixed, ready-to-use levofloxacin solution in D_5W for single-use. The fill volume is either 50 or 100 mL for the 100 mL flexible container or 150 mL for the 150 mL container. **NO FURTHER DILUTION OF THESE PREPARATIONS ARE NECESSARY. Consequently each 50 mL, 100 mL, and 150 mL premix flexible container already contains a dilute solution with the equivalent of 250 mg, 500 mg, and 750 mg of levofloxacin, respectively (5 mg/mL) in 5% Dextrose (D_5W).**

This parenteral drug product should be inspected visually for particulate matter prior to administration. Samples containing visible particles should be discarded.

Since the premix flexible containers are for single-use only, any unused portion should be discarded.

Since only limited data are available on the compatibility of levofloxacin intravenous injection with other intravenous substances, **additives or other medications should not be added to LEVAQUIN Injection in flexible containers or infused simultaneously through the same intravenous line.** If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of LEVAQUIN Injection with an infusion solution compatible with LEVAQUIN Injection and with any other drug(s) administered via this common line.

Instructions for the Use of LEVAQUIN Injection Premix in Flexible Containers

To open:

1. Tear outer wrap at the notch and remove solution container.

2. Check the container for minute leaks by squeezing the inner bag firmly. If leaks are found, or if the seal is not intact, discard the solution, as the sterility may be compromised.

3. Do not use if the solution is cloudy or a precipitate is present.

4. Use sterile equipment.

5. **WARNING: Do not use flexible containers in series connections.** Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for administration:

1. Close flow control clamp of administration set.

2. Remove cover from port at bottom of container.

3. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. **NOTE: See full directions on administration set carton.**

4. Suspend container from hanger.

5. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion of LEVAQUIN Injection in Premix Flexible Containers.

6. Open flow control clamp to expel air from set. Close clamp.

7. Regulate rate of administration with flow control clamp.

Stability of LEVAQUIN Injection as Supplied

When stored under recommended conditions, LEVAQUIN Injection, as supplied in 20 mL and 30 mL vials, or 100 mL and 150 mL flexible containers, is stable through the expiration date printed on the label.

Stability of LEVAQUIN Injection Following Dilution

LEVAQUIN Injection, when diluted in a compatible intravenous fluid to a concentration of 5 mg/mL, is stable for 72 hours when stored at or below 25°C (77°F) and for 14 days when stored under refrigeration at 5°C (41°F) in plastic intravenous containers. Solutions that are diluted in a compatible intravenous solution and frozen in glass bottles or plastic intravenous containers are stable for 6 months when stored at -20°C (-4°F). **THAW FROZEN SOLUTIONS AT ROOM TEMPERATURE 25°C (77°F) OR IN A REFRIGERATOR 8°C (46°F). DO NOT FORCE THAW BY MICROWAVE IRRADIATION OR WATER BATH IMMERSION. DO NOT REFREEZE AFTER INITIAL THAWING.**

HOW SUPPLIED

LEVAQUIN Tablets

LEVAQUIN (levofloxacin) Tablets are supplied as 250, 500, and 750 mg modified rectangular, film-coated tablets. LEVAQUIN Tablets are packaged in bottles and in unit-dose blister strips

in the following configurations:

250 mg tablets: color: terra cotta pink

debossing: "LEVAQUIN" on side 1 and "250" on side 2

bottles of 50 (NDC 0045-1520-50)

unit-dose/100 tablets (NDC 0045-1520-10)

500 mg tablets: color: peach

debossing: "LEVAQUIN" on side 1 and "500" on side 2

bottles of 50 (NDC 0045-1525-50)

unit-dose/100 tablets (NDC 0045-1525-10)

750 mg tablets: color: white

debossing: "LEVAQUIN" on side 1 and "750" on side 2

bottles of 50 (NDC 0045-1530-50)

unit-dose/100 tablets (NDC 0045-1530-10)

LEVAQUIN Tablets should be stored at 15° to 30°C (59° to 86°F) in well-closed containers.

LEVAQUIN Tablets are manufactured for OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC. by Janssen Ortho LLC, Gurabo, Puerto Rico 00778.

LEVAQUIN Injection

Single-Use Vials: LEVAQUIN (levofloxacin) Injection is supplied in single-use vials. Each vial contains a concentrated solution with the equivalent of 500 mg of levofloxacin in 20 mL vials and 750 mg of levofloxacin in 30 mL vials.

25 mg/mL, 20 mL vials (NDC 0045-0069-51)

25 mg/mL, 30 mL vials (NDC 0045-0065-55)

LEVAQUIN Injection in Single-Use Vials should be stored at controlled room temperature and protected from light.

LEVAQUIN Injection in Single-Use Vials is manufactured for OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC. by OMJ Pharmaceuticals, Inc., San German, Puerto

Rico, 00683.

Premix in Flexible Containers: LEVAQUIN (levofloxacin in 5% dextrose) Injection is supplied as a single-use, premixed solution in flexible containers. Each bag contains a dilute solution with the equivalent of 250, 500, or 750 mg of levofloxacin, respectively, in 5% Dextrose (D_5W).

5 mg/mL (250 mg), 50 mL flexible container (NDC 0045-0067-01)

5 mg/mL (500 mg), 100 mL flexible container (NDC 0045-0068-01)

5 mg/mL (750 mg), 150 mL flexible container (NDC 0045-0066-01)

LEVAQUIN Injection Premix in Flexible Containers should be stored at or below 25°C (77°F); however, brief exposure up to 40°C (104°F) does not adversely affect the product. Avoid excessive heat and protect from freezing and light.

LEVAQUIN Injection Premix in Flexible Containers is manufactured for OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC. by ABBOTT Laboratories, North Chicago, IL 60064.

CLINICAL STUDIES

Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a multicenter, randomized, open-label study comparing intravenous levofloxacin (750 mg once daily) followed by oral levofloxacin (750 mg once daily) for a total of 7-15 days to intravenous imipenem/cilastatin (500-1000mg q6-8 hours daily) followed by oral ciprofloxacin (750 mg q12 hours daily) for a total of 7-15 days. Levofloxacin-treated patients received an average of 7 days of intravenous therapy (range: 1-16 days); comparator-treated patients received an average of 8 days intravenous therapy (range 1-19 days).

Overall, in the clinically and microbiologically evaluable population, adjunctive therapy was empirically initiated at study entry in 56 of 93 (60.2%) patients in the levofloxacin arm and 53 of 94 (56.4%) patients in the comparator arm. The average duration of adjunctive therapy was 7 days in the levofloxacin arm and 7 days in the comparator. In clinically and microbiologically evaluable patients with documented *Pseudomonas aeruginosa* infection, 15 of 17 (88.2%) received ceftazidime (N=11) or piperacillin/tazobactam (N=4) in the levofloxacin arm and 16 of 17 (94.1%) received an aminoglycoside in the comparator arm. Overall, in clinically and microbiologically evaluable patients, vancomycin was added to the treatment regimen of 37 of 93 (39.8%) patients in the levofloxacin arm and 28 of 94 (29.8%) patients in the comparator arm for suspected methicillin-resistant *S.* aureus infection.

Clinical success rates in clinically and microbiologically evaluable patients at the posttherapy visit (primary study endpoint assessed on day 3-15 after completing therapy) were 58.1% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of response rates (levofloxacin minus comparator) was [-17.2, 12.0]. The microbiological eradication rates at the posttherapy visit were 66.7% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of eradication rates (levofloxacin minus comparator) was [-8.3, 20.3]. Clinical success and microbiological eradication rates by pathogen were as follows:

Pathogen	Levofloxacin N	Levofloxacin No. (%) of Patients Microbiologic / Clinical Outcomes	Imipenem/Cilastatin N	Imipenem/Cilastatin No. (%) of Patients Microbiologic / Clinical Outcomes
MSSA[a]	21	14 (66.7) / 13 (61.9)	19	13 (68.4) / 15 (78.9)
P. aeruginosa[b]	17	10 (58.8) / 11 (64.7)	17	5 (29.4) / 7 (41.2)
S. marcescens	11	9 (81.8) / 7 (63.6)	7	2 (28.6) / 3 (42.9)
E. coli	12	10 (83.3) / 7 (58.3)	11	7 (63.6) / 8 (72.7)
K. pneumoniae[c]	11	9 (81.8) / 5 (45.5)	7	6 (85.7) / 3 (42.9)
H. influenzae	16	13 (81.3) /10 (62.5)	15	14 (93.3) / 11 (73.3)
S. pneumoniae	4	3 (75.0) / 3 (75.0)	7	5 (71.4) / 4 (57.1)

[a] Methicillin-susceptible *S. aureus*.

[b] See above text for use of combination therapy.

[c] The observed differences in rates for the clinical and microbiological outcomes may reflect other factors that were not accounted for in the study.

Community-Acquired Bacterial Pneumonia

Adult inpatients and outpatients with a diagnosis of community-acquired bacterial pneumonia were evaluated in two pivotal clinical studies. In the first study, 590 patients were enrolled in a prospective, multicenter, unblinded randomized trial comparing levofloxacin 500 mg once daily orally or intravenously for 7 to 14 days to ceftriaxone 1 to 2 grams intravenously once or in equally divided doses twice daily followed by cefuroxime axetil 500 mg orally twice daily for a total of 7 to 14 days. Patients assigned to treatment with the control regimen were allowed to receive erythromycin (or doxycycline if intolerant of erythromycin) if an infection due to atypical pathogens was suspected or proven. Clinical and microbiologic evaluations were performed during treatment, 5 to 7 days posttherapy, and 3 to 4 weeks posttherapy. Clinical success (cure plus improvement) with levofloxacin at 5 to 7 days posttherapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%). The 95% CI for the difference of response rates (levofloxacin minus comparator) was [-6, 19]. In the second study, 264 patients were enrolled in a prospective, multi-center, non-comparative trial of 500 mg levofloxacin administered orally or intravenously once daily for 7 to 14 days. Clinical success for clinically evaluable patients was 93%. For both studies, the clinical success rate in patients with atypical pneumonia due to *Chlamydia pneumoniae, Mycoplasma pneumoniae*, and *Legionella pneumophila* were 96%, 96%, and 70%, respectively. Microbiologic eradication rates across both studies were as follows:

Pathogen	No. Pathogens	Microbiologic Eradication Rate (%)
H. influenzae	55	98
S pneumoniae	83	95
S. aureus	17	88
M. catarrhalis	18	94
H. parainfluenzae	19	95
K. pneumoniae	10	100.0

Additional studies were initiated to evaluate the utility of LEVAQUIN in community-acquired pneumonia due to *S. pneumoniae,* with particular interest in penicillin-resistant strains (MIC value for penicillin —2 μg/mL). In addition to the studies previously discussed, inpatients and outpatients with mild to severe community-acquired pneumonia were evaluated in six additional clinical studies; one double-blind study, two open label randomized studies, and three open label non-comparative studies. The total number of clinically evaluable patients with *S.pneumoniae* across all 8 studies was 250 for levofloxacin and 41 for comparators. The clinical success rate (cured or improved) among the 250 levofloxacin-treated patients with *S. pneumoniae* was 245/250 (98%). The clinical success rate among the 41 comparator-treated

patients with *S. pneumoniae* was 39/41 (95%).

Across these 8 studies, 18 levofloxacin-treated and 4 non-quinolone comparator-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae* (MIC value for penicillin —2 μg/mL) were identified. Of the 18 levofloxacin-treated patients, 15 were evaluable following the completion of therapy. Fifteen out of the 15 evaluable levofloxacin-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae* achieved clinical success (cure or improvement). Of these 15 patients, 6 were bacteremic and 5 were classified as having severe disease. Of the 4 comparator-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae*, 3 were evaluable for clinical efficacy. Three out of the 3 evaluable comparator-treated patients achieved clinical success. All three of the comparator-treated patients were bacteremic and had disease classified as severe.

Complicated Skin and Skin Structure Infections

Three hundred ninety-nine patients were enrolled in an open-label, randomized, comparative study for complicated skin and skin structure infections. The patients were randomized to receive either levofloxacin 750mg QD (IV followed by oral), or an approved comparator for a median of 10 ± 4.7 days. As is expected in complicated skin and skin structure infections, surgical procedures were performed in the levofloxacin and comparator groups. Surgery (incision and drainage or debridement) was performed on 45% of the levofloxacin treated patients and 44% of the comparator treated patients, either shortly before or during antibiotic treatment and formed an integral part of therapy for this indication.

Among those who could be evaluated clinically 2-5 days after completion of study drug, overall success rates (improved or cured) were 116/138 (84.1%) for patients treated with levofloxacin and 106/132 (80.3%) for patients treated with the comparator.

Success rates varied with the type of diagnosis ranging from 68% in patients with infected ulcers to 90% in patients with infected wounds and abscesses. These rates were equivalent to those seen with comparator drugs.

Chronic Bacterial Prostatitis

Adult patients with a clinical diagnosis of prostatitis and microbiological culture results from urine sample collected after prostatic massage (VB_3) or expressed prostatic secretion (EPS) specimens obtained via the Meares-Stamey procedure were enrolled in a multicenter, randomized, double-blind study comparing oral levofloxacin 500 mg, once daily for a total of 28 days to oral ciprofloxacin 500 mg, twice daily for a total of 28 days. The primary efficacy endpoint was microbiologic efficacy in microbiologically evaluable patients A total of 136 and 125 microbiologically evaluable patients were enrolled in the levofloxacin and ciprofloxacin groups, respectively. The microbiologic eradication rate by patient infection at 5-18 days after completion of therapy was 75.0% in the levofloxacin group and 76.8% in the ciprofloxacin group (95% CI [-12.58, 8.98] for levofloxacin minus ciprofloxacin). The overall eradication rates for pathogens of interest are presented below:

	Levofloxacin (N=136)		Ciprofloxacin (=125)	
Pathogen	N	Eradication	N	Eradication
E. coli	15	14 (93.3%)	11	9 (81.8%)
E. faecalis	54	39 (72.2%)	44	33 (75.0%)
**S. epidermidis*	11	9 (81.8%)	14	11 (78.6%)

*Eradication rates shown are for patients who had a sole pathogen only; mixed cultures were excluded.

Eradication rates for *S. epidermidis* when found with other co-pathogens are consistent with rates seen in pure isolates.

Clinical success (cure + improvement with no need for further antibiotic therapy) rates in microbiologically evaluable population 5-18 days after completion of therapy were 75.0% for levofloxacin-treated patients and 72.8% for ciprofloxacin-treated patients (95% CI [-8.87, 13.27] for levofloxacin minus ciprofloxacin). Clinical long-term success (24-45 days after completion of therapy) rates were 66.7% for the levofloxacin-treated patients and 76.9% for the ciprofloxacin-treated patients (95% CI [-23.40, 2.89] for levofloxacin minus ciprofloxacin).

ANIMAL PHARMACOLOGY

Levofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See **WARNINGS**.) In immature dogs (4 - 5 months old), oral doses of 10 mg/kg/day for 7 days and intravenous doses of 4 mg/kg/day for 14 days of levofloxacin resulted in arthropathic lesions. Administration at oral doses of 300 mg/kg/day for 7 days and intravenous doses of 60 mg/kg/day for 4 weeks produced arthropathy in juvenile rats.

When tested in a mouse ear swelling bioassay, levofloxacin exhibited phototoxicity similar in

magnitude to ofloxacin, but less phototoxicity than other quinolones.

While crystalluria has been observed in some intravenous rat studies, urinary crystals are not formed in the bladder, being present only after micturition and are not associated with nephrotoxicity.

In mice, the CNS stimulatory effect of quinolones is enhanced by concomitant administration of non-steroidal anti-inflammatory drugs.

In dogs, levofloxacin administered at 6 mg/kg or higher by rapid intravenous injection produced hypotensive effects. These effects were considered to be related to histamine release.

In vitro and in vivo studies in animals indicate that levofloxacin is neither an enzyme inducer or inhibitor in the human therapeutic plasma concentration range; therefore, no drug metabolizing enzyme-related interactions with other drugs or agents are anticipated.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically ~~Fifth~~ Sixth Edition. Approved Standard NCCLS Document M7 ~~A5~~ A6, Vol. ~~20~~ 23, No. 2, NCCLS, Wayne, PA, January, ~~2000~~ 2003.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests ~~Seventh~~ Eighth Edition. Approved Standard NCCLS Document M2-~~A7~~ A8, Vol. ~~20~~ 23, No. 1, NCCLS, Wayne, PA, January, ~~2000~~ 2003.

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OMP DIVISION
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APPROVED

TROVAN™ Tablets
(trovafloxacin mesylate)
TROVAN™ I.V.
(alatrofloxacin mesylate injection)
For Intravenous Infusion

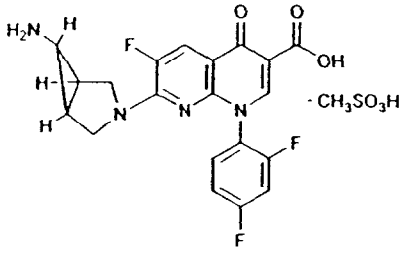
TROVAN is available as TROVAN Tablets (trovafloxacin mesylate) for oral administration and as TROVAN I.V. (alatrofloxacin mesylate injection), a prodrug of trovafloxacin, for intravenous administration.

DESCRIPTION

TROVAN Tablets

TROVAN Tablets contain trovafloxacin mesylate, a synthetic broad-spectrum antibacterial agent for oral administration. Chemically, trovafloxacin mesylate, a fluoronaphthyridone related to the fluoroquinolone antibacterials, is (1α, 5α, 6α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate. Trovafloxacin mesylate differs from other quinolone derivatives by having a 1,8-naphthyridine nucleus.

The chemical structure is:



Its empirical formula is $C_{20}H_{15}F_3N_4O_3 \bullet CH_3SO_3H$ and its molecular weight is 512.46.

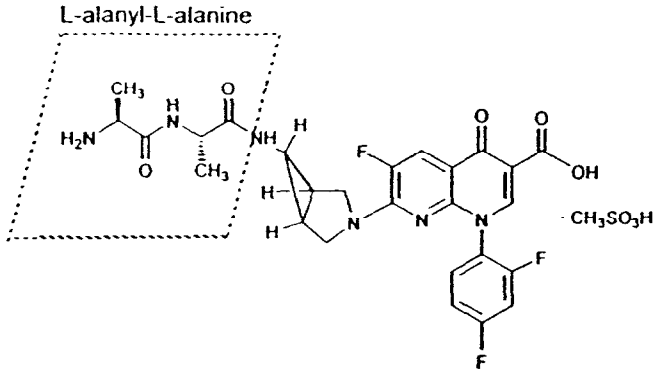
Trovafloxacin mesylate is a white to off-white powder.
Trovafloxacin mesylate is available in 100 mg and 200 mg (trovafloxacin equivalent) blue, film-coated tablets. TROVAN Tablets contain microcrystalline cellulose, crosslinked sodium carboxymethylcellulose and magnesium stearate. The tablet coating is a mixture of hydroxypropylcellulose, hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol and FD&C blue #2 aluminum lake.

TROVAN I.V.

TROVAN I.V. contains alatrofloxacin mesylate, the L-alanyl-L-alanyl prodrug of trovafloxacin mesylate. Chemically, alatrofloxacin mesylate is (1α, 5α, 6α)-L-alanyl-*N*-[3-[6-carboxy-8-(2,4-difluorophenyl)-3-fluoro-5,8-dihydro-5-oxo-1,8-naphthyridin-2-yl]-3-azabicyclo[3.1.0]hex-6-yl]-L-alaninamide, monomethanesulfonate. It is intended for administration by intravenous infusion.

Following intravenous administration, the alanine substituents in alatrofloxacin are rapidly hydrolyzed *in vivo* to yield trovafloxacin. (See **CLINICAL PHARMACOLOGY**)

The chemical structure is:



Its empirical formula is $C_{26}H_{25}F_3N_6O_5 \bullet CH_3SO_3H$ and its molecular weight is 654.62.

Alatrofloxacin mesylate is a white to light yellow powder.

TROVAN I.V. is available in 40 mL and 60 mL single use vials as a sterile, preservative-free aqueous concentrate of 5 mg trovafloxacin/mL as alatrofloxacin mesylate intended for dilution prior to intravenous administration of doses of 200 mg or 300 mg of trovafloxacin, respectively. (See **HOW SUPPLIED.)**

The formulation contains Water for Injection, and may contain sodium hydroxide or hydrochloric acid for pH adjustment.
The pH range for the 5 mg/mL aqueous concentrate is 3.5 to 4.3.

CLINICAL PHARMACOLOGY

After intravenous administration, alatrofloxacin is rapidly converted to trovafloxacin. Plasma concentrations of alatrofloxacin are below quantifiable levels within 5 to 10 minutes of completion of a one hour infusion.

Absorption

Trovafloxacin is well-absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 88%. For comparable dosages, no dosage adjustment is necessary when switching from parenteral to oral administration (Figure 1). (See **DOSAGE AND ADMINISTRATION.)**

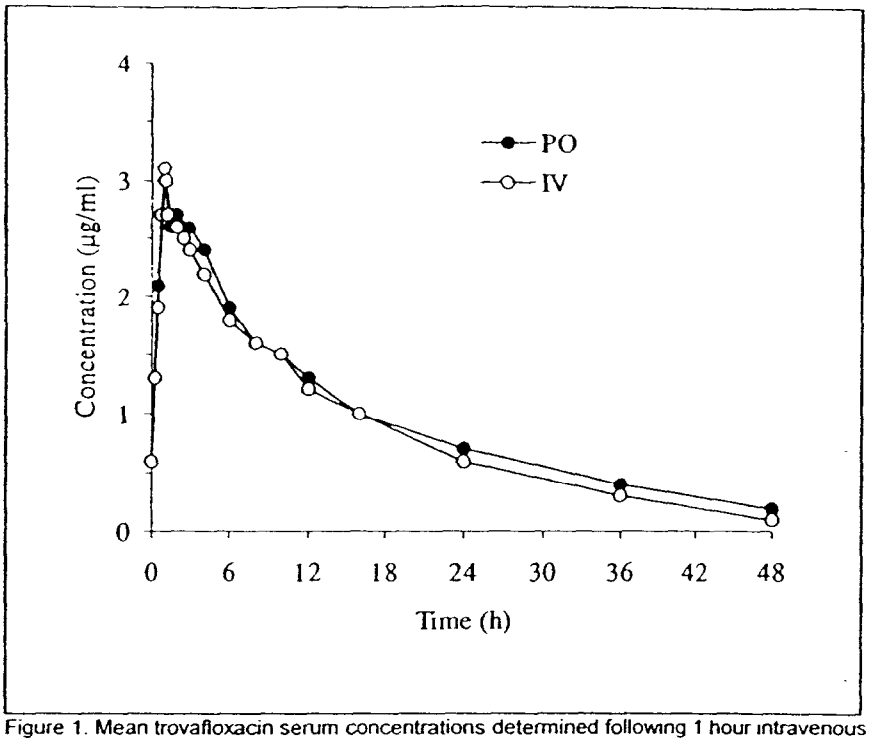


Figure 1. Mean trovafloxacin serum concentrations determined following 1 hour intravenous infusions of alatrofloxacin at daily doses of 200 mg (trovafloxacin equivalents) to healthy male volunteers and following daily oral administration of 200 mg trovafloxacin for seven days to six male and six female healthy young volunteers.

Pharmacokinetics

The mean pharmacokinetic parameters (±SD) of trovafloxacin after single and multiple 100 mg and 200 mg oral doses and one hour intravenous infusions of alatrofloxacin in doses of 200 and 300 mg (trovafloxacin equivalents) appear in the chart below.

TROVAFLOXACIN PHARMACOKINETIC PARAMETERS

	C_{max} (µg/mL)	T_{max} (hrs)	AUC[1,2] (µg•h/mL)	$T_{1/2}$ (hrs)	V_{dss} (L/Kg)	CL (mL/hr/Kg)	CL_r (mL/hr/Kg)
Trovafloxacin 100 mg							
Single dose	1.0±0.3	0.9±0.4	11.2±2.2	9.1	—	—	—
Multiple dose	1.1±0.2	1.0±0.5	11.8±1.8	10.5	—	—	—
Trovafloxacin 200 mg							
Single dose	2.1±0 5	1.8±0.9	26.7±7.5	9.6	—	—	—
Multiple dose	3.1±.1.0	1.2±0.5	34.4±5.7	12.2	—	—	—
Alatrofloxacin 200 mg*							
Single dose	2.7±0.4	1.0±0.0	28.1±5.1	9.4	1.2±0.2	93.0±17.4	6.5±3.5
Multiple dose	3.1±0.6	1.0±0.0	32.2±7.3	11.7	1.3±0.1	81.7±17.8	8 6±2.4
Alatrofloxacin 300 mg*							
Single dose	3.6±0.6	1.3±0 4	46.1±5.2	11.2	1.2±0.1	84.6±6.0	6.9±0.5
Multiple dose	4.4±0.6	1.2±0.2	46.3±3.9	12 7	1.4±0.1	84.5±11.1	8 4±1.8

*trovafloxacin equivalents

[1,2] Single dose: AUC(0-∞), multiple dose: AUC(0-24)

C_{max}= Maximum serum concentration; T_{max}=Time to C_{max}; AUC=Area under concentration vs. time curve; $T_{1/2}$=serum half-life; V_{ss}=Volume of distribution; Cl=Total clearance, Cl_r=Renal clearance

Serum concentrations of trovafloxacin are dose-proportional after oral administration of trovafloxacin in the dose range of 30 to 1000 mg or after intravenous administration of

alatrofloxacin in the dose range of 30 to 400 mg (trovafloxacin equivalents). Steady state concentrations are achieved by the third daily oral or intravenous dose of trovafloxacin with an accumulation factor of approximately 1.3 times the single dose concentrations.

Oral absorption of trovafloxacin is not altered by concomitant food intake; therefore, it can be administered without regard to food.

The systemic exposure to trovafloxacin ($AUC_{0-\infty}$) administered as crushed tablets via nasogastric tube into the stomach was identical to that of orally administered intact tablets. Administration of concurrent enteral feeding solutions had no effect on the absorption of trovafloxacin given via nasogastric tube into the stomach. When trovafloxacin was administered as crushed tablets into the duodenum via nasogastric tube, the $AUC_{0-\infty}$ and peak serum concentration (Cmax) were reduced by 30% relative to the orally administered intact tablets. Time to peak serum level (Tmax) was also decreased from 1.7 hrs to 1.1 hrs..

Distribution

The mean plasma protein bound fraction is approximately 76%, and is concentration-independent. Trovafloxacin is widely distributed throughout the body. Rapid distribution of trovafloxacin into tissues results in significantly higher trovafloxacin concentrations in most target tissues than in plasma or serum.

Fluid or Tissue	Tissue-Fluid/-Serum Ratio* (Range)
Respiratory	
bronchial macrophages (multiple dose)	24.1 (9.6-41.8)
lung mucosa	1.1(0.7-1.5)
lung epithelial lining fluid (multiple dose)	5.8 (1.1-17.5)
whole lung	2.1 (0.42-5.03)
Skin, Musculoskeletal	
skin	1.0 (0.20-1.88)
subcutaneous tissue	0.4 (0.15-0.68)
skin blister fluid	0.7-0.9 (blister/plasma)
skeletal muscle	1.5 (0.50-2.90)
bone	1.0 (0.55-1.67)
Gastrointestinal	
colonic tissue	0.7 (0.0-1.47)
peritoneal fluid	0.4 (0.0-1.25)
bile	15.4 (11.9-21.0)
Central Nervous System	
cerebrospinal fluid (CSF), adults	0.25 (0.03-0.33)
cerebrospinal fluid (CSF), children	0.28**
Reproductive	
prostatic tissue	1.0 (0.5-1.6)
cervix (multiple dose)	0.6 (0.5-0.7)
ovary	1.6 (0.3-2.2)
fallopian tube	0.7 (0.2-1.1)
myometrium (multiple dose)	0.6 (0.4-0.8)
uterus	0.6 (0.3-0.8)
vaginal fluid (multiple dose)	4.7 (0.8-20.8)

* Mean values in adults over 2-29 hours following drug administration, except individual lung tissues, which were single time points of 6 hours following drug administration

** Ratio of composite AUC(0-24) in CSF/composite AUC(0-24) in serum in 22 pediatric patients aged 1 to 12 years after 1 hour i.v. infusion of single dose alatrofloxacin (equivalent trovafloxacin dose range: 4.5-9.9 mg/kg)

Presence in Breast Milk

Trovafloxacin was found in measurable concentrations in the breast milk of three lactating subjects. The average measurable breast milk concentration was 0.8 μg/mL (range: 0.3-2.1 μg/mL) after single i.v. alatrofloxacin (300 mg trovafloxacin equivalents) and repeated oral trovafloxacin (200 mg) doses.

Metabolism

Trovafloxacin is metabolized by conjugation (the role of cytochrome P_{450} oxidative metabolism of trovafloxacin is minimal). Thirteen percent of the administered dose appears in the urine in the form of the ester glucuronide and 9% appears in the feces as the N-acetyl metabolite (2.5% of the dose is found in the serum as the active N-acetyl metabolite). Other minor metabolites (diacid, sulfamate, hydroxycarboxylic acid) have been identified in both urine and feces in small amounts (<4% of the administered dose)..

Excretion

Approximately 50% of an oral dose is excreted unchanged (43 % in the feces and 6% in the urine).

After multiple 200 mg doses, to healthy subjects, mean (± SD) cumulative urinary trovafloxacin concentrations were 12.1 ±3.4 μg/mL. With these levels of trovafloxacin in urine, crystals of trovafloxacin have not been observed in the urine of human subjects.

Special Populations

Geriatric

In adult subjects, the pharmacokinetics of trovafloxacin are not affected by age (range 19-78 years).

Pediatric

Limited information is available in the pediatric population (See **Distribution**). The pharmacokinetics of trovafloxacin have not been fully characterized in pediatric populations less than 18 years of age.

Gender

There are no significant differences in trovafloxacin pharmacokinetics between males and females when differences in body weight are taken into account. After single 200 mg doses, trovafloxacin Cmax and AUC(0-∞) were 60% and 32% higher, respectively, in healthy females compared to healthy males. Following repeated daily administration of 200 mg for 7 days, the Cmax for trovafloxacin was 38% higher and AUC(0-24) was 16% higher in healthy females compared to healthy males. The clinical importance of the increases in serum levels of trovafloxacin in females has not been established. (See **PRECAUTIONS: Information for Patients**).

Chronic Hepatic Disease

Following repeated administration of 100 mg for 7 days to patients with mild cirrhosis (Child-Pugh Class A), the AUC(0-24) for trovafloxacin was increased ~45% compared to matched controls. Repeated administration of 200 mg for 7 days to patients with moderate cirrhosis (Child-Pugh Class B) resulted in an increase of ~50% in AUC(0-24) compared to matched controls. There appeared to be no significant effect on trovafloxacin Cmax for either group. The oral clearance of trovafloxacin was reduced ~30% in both cirrhosis groups, which corresponded to prolongation of half-life by 2-2.5 hours (25-30% increase) compared to

controls. There are no data in patients with severe cirrhosis (Child-Pugh Class C). Dosage adjustment is recommended in patients with mild to moderate cirrhosis. **(See DOSAGE AND ADMINISTRATION)**

Renal Insufficiency

The pharmacokinetics of trovafloxacin are not affected by renal impairment. Trovafloxacin serum concentrations are not significantly altered in subjects with severe renal insufficiency (creatinine clearance < 20 mL/min), including patients on hemodialysis.

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 48 healthy volunteers (12 per group), the minimum erythematous dose (MED) was measured for ciprofloxacin, lomefloxacin, trovafloxacin and placebo before and after drug administration for 5 days. In this study, trovafloxacin (200 mg q.d.) was shown to have a lower potential for producing delayed photosensitivity skin reactions than ciprofloxacin (500 mg b.i.d.) or lomefloxacin (400 mg q.d.), although greater than placebo. (See **PRECAUTIONS: Information for Patients)**

Drug-drug Interactions

The systemic availability of trovafloxacin following oral tablet administration is significantly reduced by the concomitant administration of antacids containing aluminum and magnesium salts, sucralfate, vitamins or minerals containing iron, and concomitant intravenous morphine administration.

Administration of trovafloxacin (300 mg p.o.) 30 minutes after administration of an antacid containing magnesium hydroxide and aluminum hydroxide resulted in reductions in systemic exposure to trovafloxacin (AUC) of 66% and peak serum concentration (Cmax) of 60%. (See **PRECAUTIONS: Drug Interactions, DOSAGE AND ADMINISTRATION)**

Concomitant sucralfate administration (1g) with trovafloxacin 200 mg p.o. resulted in a 70% decrease in trovafloxacin systemic exposure (AUC) and a 77% reduction in peak serum concentration (Cmax). (See **PRECAUTIONS: Drug Interactions, DOSAGE AND ADMINISTRATION)**

Concomitant administration of ferrous sulfate (120 mg elemental iron) with trovafloxacin 200 mg p.o. resulted in a 40% reduction in trovafloxacin systemic exposure (AUC) and a 48% decrease in trovafloxacin Cmax. (See **PRECAUTIONS: Drug Interactions, DOSAGE AND ADMINISTRATION)**

Concomitant administration of intravenous morphine (0.15 mg/kg) with oral trovafloxacin (200 mg) resulted in a 36% reduction in trovafloxacin AUC and a 46% decrease in trovafloxacin Cmax. Trovafloxacin administration had no effect on the pharmacokinetics of morphine or its pharmacologically active metabolite, morphine-6-β-glucuronide. (See **PRECAUTIONS: Drug Interactions, DOSAGE AND ADMINISTRATION)**

Minor pharmacokinetic interactions that are most likely without clinical significance include calcium carbonate, omeprazole and caffeine.

Concomitant administration of calcium carbonate (1000 mg) with trovafloxacin 200 mg p.o. resulted in a 20% reduction in trovafloxacin AUC and a 17% reduction in peak serum trovafloxacin concentration (Cmax).

A 40 mg dose of omeprazole given 2 hours prior to trovafloxacin (300 mg p.o.) resulted in a 17% reduction in trovafloxacin AUC and a 17% reduction in trovafloxacin peak serum concentration (Cmax).

Administration of trovafloxacin (200 mg) concomitantly with caffeine (200 mg) resulted in a 17% increase in caffeine AUC and a 15% increase in caffeine Cmax. These changes in caffeine exposure are not considered clinically significant.

No significant pharmacokinetic interactions include cimetidine, theophylline, digoxin, warfarin and cyclosporine.

Cimetidine co-administration (400 mg twice daily for 5 days) with trovafloxacin (200 mg p.o. daily for 3 days) resulted in changes in trovafloxacin AUC and Cmax of less than 5%.

Trovafloxacin (200 mg p.o. daily for 7 days) co-administration with theophylline (300 mg twice daily for 14 days) resulted in no change in theophylline AUC and Cmax.

Trovafloxacin (200 mg p.o. daily for 10 days) co-administration with digoxin (0.25 mg daily for 20 days) did not significantly alter systemic exposure (AUC) to digoxin or the renal clearance of digoxin.

Trovafloxacin (200 mg p.o. daily for 7 days) does not interfere with the pharmacokinetics nor the pharmacodynamics of warfarin (daily for 21 days). Concomitant oral administration of trovafloxacin did not affect the systemic exposure (AUC) or peak plasma concentrations (Cmax) of the S or R isomers of warfarin, nor did it influence prothrombin times.

Trovafloxacin (200 mg p.o. daily for 7 days) co-administration with cyclosporine (daily doses from 150-450 mg for 7 days) resulted in decreases of 10% or less in systemic exposure to cyclosporine (AUC) and in the peak blood concentrations of cyclosporine.

Microbiology

Trovafloxacin is a fluoronaphthyridone related to the fluoroquinolones with *in vitro* activity against a wide range of gram-negative and gram-positive aerobic, and anaerobic microorganisms. The bactericidal action of trovafloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. Mechanism of action of fluoroquinolones including trovafloxacin is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines. Therefore, fluoroquinolones may be active against pathogens that are resistant to these antibiotics. There is no cross-resistance between trovafloxacin and the mentioned classes of antibiotics. The overall results obtained from *in vitro* synergy studies, testing combinations of trovafloxacin with beta-lactams and aminoglycosides, indicate that synergy is strain specific and not commonly encountered. This agrees with results obtained previously with other fluoroquinolones. Resistance to trovafloxacin *in vitro* develops slowly via multiple-step mutation in a manner similar to other fluoroquinolones. Resistance to trovafloxacin *in vitro* occurs at a general frequency of between $1x10^{-7}$ to 10^{-10}. Although cross-resistance has been observed between trovafloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to trovafloxacin.

Trovafloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-positive microorganisms
Enterococcus faecalis (many strains are only moderately susceptible)
Staphylococcus aureus (methicillin-susceptible strains)
Staphylococcus epidermidis (methicillin-susceptible strains)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes
Viridans group streptococci

Aerobic gram-negative microorganisms
Escherichia coli
Gardnerella vaginalis
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Neisseria gonorrhoeae
Proteus mirabilis
Pseudomonas aeruginosa

Anaerobic microorganisms
Bacteroides fragilis
Peptostreptococcus species
Prevotella species

Other microorganisms
Chlamydia pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown.**

Trovafloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of ≤2 µg/mL against most (90%) strains of the following microorganisms; however, the safety and effectiveness of trovafloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-positive microorganisms
Streptococcus pneumoniae (penicillin-resistant strains)

Aerobic Gram-negative microorganisms
Citrobacter freundii
Enterobacter aerogenes
Morganella morganii
Proteus vulgaris

Anaerobic microorganisms

Bacteroides distasonis
Bacteroides ovatus
Clostridium perfringens

Other microorganisms
Mycoplasma hominis
Ureaplasma urealyticum

NOTE: *Mycobacterium tuberculosis* and *Mycobacterium avium-intracellulare* complex organisms are commonly resistant to trovafloxacin.
NOTE: The activity of trovafloxacin against *Treponema pallidum* has not been evaluated; however, other quinolones are not active against *Treponema pallidum*. (See WARNINGS.)

Susceptibility Tests:

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of trovafloxacin mesylate powder. The MIC values should be interpreted according to the following criteria:

For testing non-fastidious aerobic organisms

MIC (µg/mL)	Interpretation
≤ 2.0	Susceptible (S)
4.0	Intermediate (I)
≥ 8.0	Resistant (R)

For testing *Haemophilus* spp.[a]:

MIC (µg/mL)	Interpretation[b]
≤ 1.0	Susceptible (S)

[a] These interpretive standards are applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using Haemophilus Test Medium (HTM)[1]
[b] The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* spp. including *Streptococcus pneumoniae*[c]:

MIC (µg/mL)	Interpretation
≤ 1.0	Susceptible (S)
2.0	Intermediate (I)
≥ 4.0	Resistant (R)

[c] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2 - 5 % lysed horse blood.

For testing *Neisseria gonorrhoeae*[d]:

MIC (µg/mL)	Interpretation
≤ 0.125	Susceptible (S)
0.25	Intermediate (I)
≥ 0.5	Resistant (R)

[d] These interpretive standards are applicable to agar dilution tests with GC agar base and 1% defined growth supplement[1].

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected. Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard trovafloxacin mesylate powder should provide the following MIC values:

Microorganism	MIC Range (µg/mL)
Escherichia coli ATCC 25922	0.004-0.016
Staphylococcus aureus ATCC 29213	0.008-0.03
Pseudomonas aeruginosa ATCC 27853	0.25-2.0
Enterococcus faecalis ATCC 29212	0.06-0.25
Haemophilus influenzae[e] ATCC 49247	0.004-0.016
Streptococcus pneumoniae[f] ATCC 49619	0.06-0.25
Neisseria gonorrhoeae[g] ATCC 49226	0.004-0.016

[e] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a microdilution procedure using HTM[1].

[f] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

[g] This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base with 1% defined growth supplement[1]

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with trovafloxacin mesylate equivalent to 10 µg trovafloxacin to test the susceptibility of microorganisms to trovafloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a trovafloxacin mesylate disk (equivalent to 10 µg trovafloxacin) should be interpreted according to the following criteria:

The following zone diameter interpretive criteria should be used for testing non-fastidious aerobic organisms:

Zone Diameter (mm)	Interpretation

≥ 17	Susceptible (S)
14-16	Intermediate (I)
≤ 13	Resistant (R)

For testing *Haemophilus* spp.[h]:

Zone Diameter (mm)	Interpretation[i]
≥ 22	Susceptible (S)

[h] These zone diameter standards are applicable only to tests with *Haemophilus* spp. using HTM[2].

[i] The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* spp. including *Streptococcus pneumoniae*[j]:

Zone Diameter (mm)	Interpretation
≥ 19	Susceptible (S)
18-16	Intermediate (I)
≤ 15	Resistant (R)

[j] These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2

For testing *Neisseria gonorrhoeae*[k]:

Zone Diameter (mm)	Interpretation
≥ 37	Susceptible (S)
34-36	Intermediate (I)
≤ 33	Resistant (R)

[k] These interpretive standards are applicable to disk diffusion tests with GC agar base and 1% defined growth supplement[2] incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for trovafloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the trovafloxacin mesylate equivalent to 10-µg trovafloxacin disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter Range (mm)
Escherichia coli ATCC 25922	29-36
Staphylococcus aureus ATCC 25923	29-35
Pseudomonas aeruginosa ATCC 27853	21-27
Haemophilus influenzae[l] ATCC 49247	32-39
Streptococcus pneumoniae[m] ATCC 49619	25-32
Neisseria gonorrhoeae[n] ATCC 49226	42-55

[l] This quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC 49247 using HTM[2].

[m] This quality control range is applicable only to tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.

[n] This quality control range is only applicable to tests performed by disk diffusion using GC agar base and 1% defined growth supplement[2].

Anaerobic techniques: For anaerobic bacteria, the susceptibility to trovafloxacin as MICs can be determined by standardized test methods[3]. The MIC values obtained should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤ 2.0	Susceptible (S)
4.0	Intermediate (I)
≥ 8.0	Resistant (R)

Interpretation is identical to that stated above for results using dilution techniques.

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standardized trovafloxacin mesylate powder should provide the following MIC values:

Microorganism	MIC[p] (µg/mL)
Bacteroides fragilis ATCC 25285	0.125-0.5
Bacteroides thetaiotaomicron ATCC 29741	0.25-1.0
Eubacterium lentum ATCC 43055	0.25-1.0

[p] These quality control ranges were derived from tests performed in the broth formulation of Wilkins-Chalgren agar.

INDICATIONS AND USAGE

TROVAN is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. (See **DOSAGE AND ADMINISTRATION**)

Nosocomial pneumonia caused by *Escherichia coli, Pseudomonas aeruginosa, Haemophilus influenzae, or Staphylococcus aureus.* As with other antimicrobials, where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with either an aminoglycoside or aztreonam may be clinically indicated.

Community acquired pneumonia caused by *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Staphylococcus aureus, Mycoplasma pneumoniae, Moraxella catarrhalis, Legionella pneumophila* or *Chlamydia pneumoniae.*

Acute bacterial exacerbation of chronic bronchitis caused by *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae, Staphylococcus aureus,* or *Haemophilus parainfluenzae.*

Acute sinusitis caused by *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.*

Complicated intra-abdominal infections, including post-surgical infections caused by *Escherichia coli, Bacteroides fragilis,* viridans group streptococci, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Peptostreptococcus* species or *Prevotella* species.

Gynecologic and pelvic infections including endomyometritis, parametritis, septic abortion and post-partum infections caused by *Escherichia coli, Bacteroides fragilis,* viridans group streptococci, *Enterococcus faecalis, Streptococcus agalactiae, Peptostreptococcus* species, *Prevotella* species or *Gardnerella vaginalis.*

Prophylaxis of infection associated with elective colorectal surgery, vaginal and abdominal hysterectomy.

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus, Streptococcus pyogenes* or *Streptococcus agalactiae.*

Complicated skin and skin structure infections, including diabetic foot infections, caused by *Staphylococcus aureus, Streptococcus agalactiae, Pseudomonas aeruginosa, Enterococcus faecalis, Escherichia coli,* or *Proteus mirabilis.* **NOTE:** TROVAN has not been studied in the treatment of osteomyelitis. The safety and efficacy of TROVAN given for >4 weeks have not been studied. (See **PRECAUTIONS: General**)

Uncomplicated urinary tract infections (cystitis) caused by *Escherichia coli.*

Chronic bacterial prostatitis caused by *Escherichia coli, Enterococcus faecalis or Staphylococcus epidermidis.*

Uncomplicated urethral gonorrhea in males and endocervical and rectal gonorrhea in females caused by *Neisseria gonorrhoeae.* (See **WARNINGS.**)

Cervicitis due to *Chlamydia trachomatis.* **NOTE:** In males with nongonococcal urethritis TROVAN was somewhat less effective than doxycycline.

Pelvic inflammatory disease (mild to moderate) caused by *Neisseria gonorrhoeae* or *Chlamydia trachomatis.*

CONTRAINDICATIONS

TROVAN is contraindicated in persons with a history of hypersensitivity to trovafloxacin, alatrofloxacin, quinolone antimicrobial agents or any other components of these products.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF TROVAFLOXACIN IN PEDIATRIC POPULATIONS LESS THAN 18 YEARS OF AGE, PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pediatric Use, Pregnancy,** and **Nursing Mothers** subsections.)

As with other members of the quinolone class, trovafloxacin has caused arthropathy and/or chondrodysplasia in immature rats and dogs. The significance of these findings to humans is unknown. (See **ANIMAL PHARMACOLOGY.**)

Convulsions, increased intracranial pressure and psychosis have been reported in patients receiving quinolones. Quinolones may also cause central nervous system stimulation which may lead to tremors, restlessness, lightheadedness, confusion, hallucinations, paranoia,

depression, nightmares and insomnia. These reactions may occur following the first dose. If these reactions occur in patients receiving trovafloxacin or alatrofloxacin, the drug should be discontinued and appropriate measures instituted. (See PRECAUTIONS: General, Information for Patients, Drug Interactions and ADVERSE REACTIONS.)

As with other quinolones, TROVAN should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral atherosclerosis, epilepsy, and other factors that predispose to seizures. (See ADVERSE REACTIONS.)

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones. These reactions may occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria, itching and other serious skin reactions.

TROVAN should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated. (See **PRECAUTIONS** and **ADVERSE REACTIONS.)**

Serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology have been reported in patients receiving therapy with all antibiotics. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial nephritis; acute renal insufficiency or failure; hepatitis, jaundice, acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including TROVAN, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. (See **ADVERSE REACTIONS.)**

Although not seen in TROVAN clinical trials, ruptures of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones. TROVAN should be discontinued if the patient experiences pain, inflammation or rupture of a tendon. Patients should rest and refrain from exercise

until the diagnosis of tendinitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones.

Trovafloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis.

PRECAUTIONS

General:

Because TROVAN can cause elevations of liver function tests during or soon after prolonged therapy (i.e., ≥21 days), periodic assessment of hepatic function is advisable. The safety and efficacy of TROVAN given for >4 weeks have not been studied. (See **ADVERSE REACTIONS**)

Moderate to severe phototoxicity reactions have been observed in patients who are exposed to direct sunlight while receiving some drugs in this class. Therapy should be discontinued if phototoxicity (e.g., a skin eruption, etc.) occurs.

The safety and efficacy of TROVAN in patients with severe cirrhosis (Child-Pugh Class C) have not been studied.

Information for Patients:

Patients should be advised:

- that TROVAN Tablets may be taken without regard to meals;

- that vitamins or minerals containing iron, aluminum-, or magnesium- base antacids, antacids containing citric acid buffered with sodium citrate, or sucralfate should be taken at least two hours before or two hours after taking TROVAN Tablets. (See **Drug Interactions.**);

- that TROVAN may cause lightheadedness and/or dizziness. Dizziness and/or lightheadedness was the most common adverse reaction reported, and for females under 45 years, it was reported significantly more frequently than in other groups. The incidence of dizziness may be substantially reduced if TROVAN Tablets are taken at bedtime or with food. Patients should know how they react to trovafloxacin before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination. (See **WARNINGS** and **ADVERSE REACTIONS**);

- to discontinue treatment and inform their physician if they experience pain, inflammation or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded;

- that TROVAN may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, difficulty in swallowing or breathing, any swelling suggesting angioedema, (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction. (See **WARNINGS** and **ADVERSE REACTIONS**);

- to avoid excessive sunlight or artificial ultraviolet light (e.g., tanning beds) while taking TROVAN and to discontinue therapy if phototoxicity (e.g., sunburn-like reaction or skin eruption) occurs.

Drug Interactions:

No significant interactions with theophylline, cimetidine, digoxin, warfarin or cyclosporine have been observed with TROVAN Tablets **(see CLINICAL PHARMACOLOGY)**.

Minor pharmacokinetic interactions without clinical significance have been observed with co-administration of TROVAN Tablets with caffeine, omeprazole and calcium carbonate **(see CLINICAL PHARMACOLOGY)**.

Antacids, Sucralfate, and Iron: The absorption of oral trovafloxacin is significantly reduced by the concomitant administration of some antacids containing magnesium or aluminum, citric acid/sodium citrate (Bicitra®), as well as sucralfate and iron (as ferrous ions). The above oral agents should be taken at least two hours before or two hours after oral trovafloxacin administration (see **CLINICAL PHARMACOLOGY**).

Morphine: Co-administration of intravenous morphine significantly reduces the absorption of oral trovafloxacin. Intravenous morphine should be administered at least 2 hours after oral TROVAN dosing in the fasted state and at least 4 hours after oral TROVAN is taken with

food. Trovafloxacin administration had no effect on the pharmacokinetics of morphine or its metabolite, morphine-6-β-glucuronide. (See **CLINICAL PHARMACOLOGY**).

Alatrofloxacin should not be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line. (See **DOSAGE AND ADMINISTRATION**)

Laboratory Test Interactions: There are no reported laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long term studies in animals to determine the carcinogenic potential of trovafloxacin or alatrofloxacin have not been conducted.

Trovafloxacin was not mutagenic in the Ames Salmonella reversion assay or CHO/HGPRT mammalian cell gene mutation assay and it was not clastogenic in mitogen-stimulated human lymphocytes or mouse bone marrow cells. A mouse micronucleus test conducted with alatrofloxacin was also negative. The positive response observed in the *E. coli* bacterial mutagenicity assay may be due to the inhibition of DNA gyrase by trovafloxacin.

Trovafloxacin and alatrofloxacin did not affect the fertility of male or female rats at oral and IV doses of 75 mg/kg/day and 50 mg/kg/day, respectively. These doses are 15 and 10 times the recommended maximum human dose based on mg/kg or approximately 2 times based on mg/m^2. However, oral doses of trovafloxacin at 200 mg/kg/day (40 times the recommended maximum human dose based on mg/kg or about 6 times based on mg/m^2) were associated with increased preimplantation loss in rats.

Pregnancy: Teratogenic Effects. Pregnancy Category C:

An increase in skeletal variations was observed in rat fetuses after daily oral 75 mg/kg maternal doses of trovafloxacin (approximately 15 times the highest recommended human dose based on mg/kg or twice the based upon body surface area) were administered during organogenesis. However, fetal skeletal variations were not observed in rats dosed orally with 15 mg/kg trovafloxacin. Evidence of fetotoxicity (increased perinatal morality and decreased body weights) was also observed in rats at 75 mg/kg. Daily oral doses of trovafloxacin at 45 mg/kg (approximately 9 times the highest recommended human dose based on mg/kg or 2.7 times based upon body surface area) in the rabbit were not associated with an increased incidence of fetal skeletal variations or malformations.

An increase in skeletal variations and malformations was observed in rat fetuses after daily intravenous doses of alatrofloxacin at ≥20 mg/kg/day (approximately 4 times the highest recommended human dose based on mg/kg or 0.6 times based upon body surface area) were administered to dams during organogenesis. In the rabbit, an increase in fetal skeletal malformations was also observed when 20 mg/kg/day (approximately equal to the highest recommended human dose based upon body surface area) of alatrofloxacin was given intravenously during the period of organogenesis. Intravenous dosing of alatrofloxacin at 6.5 mg/kg in the rat or rabbit was not associated with an increased incidence of skeletal variations or malformations. Fetotoxicity and fetal skeletal malformations have been associated with other quinolones.

Oral doses of trovafloxacin >5mg/kg were associated with an increased gestation time in rats and several dams at 75 mg/kg experienced uterine dystocia.

There are no adequate and well-controlled studies in pregnant women. TROVAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**)

Nursing Mothers:
Trovafloxacin is excreted in human milk and was found in measurable concentrations in the breast milk of lactating subjects (See **CLINICAL PHARMACOLOGY, Distribution**).

Because of the potential for unknown effects from trovafloxacin in nursing infants from mothers taking trovafloxacin, a decision should be made either to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
The safety and effectiveness of trovafloxacin in pediatric populations less than 18 years of age have not been established. Quinolones, including trovafloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. (See **WARNINGS**)

Geriatric Use:
In multiple-dose clinical trials of trovafloxacin, 27% of patients were ≥ 65 years of age and 12% of patients were ≥ 75 years of age. The overall incidence of drug-related adverse reactions, including central nervous system and gastrointestinal side effects, was less in the ≥65 year group than the other age groups.

ADVERSE REACTIONS
Over 6000 patients have been treated with TROVAN in multidose clinical efficacy trials worldwide.

In TROVAN studies the majority of adverse reactions were described as mild in nature (over 90% were described as mild or moderate). TROVAN was discontinued for adverse events thought related to drug in 5% of patients (dizziness 2.4%, nausea 1.9%, headache 1.1%, and vomiting 1.0%).

Trovan® Drug-Related Adverse Reactions (frequency ≥1%) in Multiple-Dose Clinical Trials

	100 mg oral qd (N=1536)	200 mg oral qd (N=3259)	200 mg IV→ 200 mg oral qd (N=634)	300 mg IV→ 200 mg oral qd (N=623)
Dizziness	3%	11%	2%	2%
Lightheadedness	2%	4%	2%	<1%
Nausea	4%	8%	5%	4%
Headache	4%	5%	5%	1%
Vomiting	<1%	3%	1%	3%
Diarrhea	2%	2%	2%	2%
Abdominal pain	<1%	1%	1%	0%
Application/ injection/ insertion site reaction	n/a	n/a	5%	2%
Vaginitis	1%	1%	<1%	<1%

Pruritus	<1%	<1%	2%	2%
Rash	<1%	<1%	2%	2%

Dizziness/lightheadedness on TROVAN is generally mild, lasts for a few hours following a dose, and in most cases, resolves with continued dosing. The incidence of dizziness and lightheadedness in TROVAN patients over 65 years is 3.1% and 0.6%, respectively. (See **PRECAUTIONS: Information for Patients)**

TROVAN appears to have a low potential for phototoxicity. In clinical trials with TROVAN, only mild, treatment-related phototoxicity was observed in less than 0.03% (2/7096) of patients.

Additional reported drug-related events in clinical trials (remotely, possibly, probably or unknown) that occurred in <1% of TROVAN-treated patients are:

APPLICATION/INJECTION/INCISION/INSERTION SITE:
Application/incision/injection/insertion site device complications, inflammation, pain, edema

AUTONOMIC NERVOUS: flushing, increased sweating, dry mouth, cold clammy skin, increased saliva

CARDIOVASCULAR: peripheral edema, chest pain, thrombophlebitis, hypotension, palpitation, periorbital edema, hypertension, syncope, tachycardia, angina pectoris, bradycardia, peripheral ischemia, edema, dizziness postural

CENTRAL & PERIPHERAL NERVOUS SYSTEM: confusion, paresthesia, vertigo, hypoesthesia, ataxia, convulsions, dysphonia, hypertonia, migraine, involuntary muscle contractions, speech disorder, encephalopathy, abnormal gait, hyperkinesia, hypokinesia, tongue paralysis, abnormal coordination, tremor, dyskinesia

GASTROINTESTINAL: abdominal pain, altered bowel habit, constipation, diarrhea-*Clostridium difficile*, dyspepsia, flatulence, loose stools, gastritis, dysphagia, increased appetite, gastroenteritis, rectal disorder, colitis, pseudomembranous colitis, enteritis, eructation, gastrointestinal disorder, melena, hiccup

ORAL CAVITY: gingivitis, stomatitis, altered saliva, tongue disorder, tongue edema, tooth disorder, chelitis, halitosis

GENERAL/OTHER: fever, fatigue, pain, asthenia, moniliasis, hot flushes, back pain, chills, infection(bacterial, fungal), malaise, sepsis, alcohol intolerance, allergic reaction, anaphylactoid reaction, drug(other) toxicity/reaction, weight increase, weight decrease

HEMATOPOIETIC: anemia, granulocytopenia, hemorrhage unspecified, leukopenia, prothrombin decreased, thrombocythemia, thrombocytopenia

LIVER/BILIARY: increased hepatic enzymes, hepatic function abnormal, bilirubinemia, discolored feces, jaundice

METABOLIC/NUTRITIONAL: hyperglycemia, thirst

MUSCULOSKELETAL: arthralgia, muscle cramps, myalgia, muscle weakness, skeletal pain, tendinitis, arthropathy

PSYCHIATRIC: anxiety, anorexia, agitation, nervousness, somnolence, insomnia, depression, amnesia, concentration impaired, depersonalization, dreaming abnormal, emotional lability, euphoria, hallucination, impotence, libido decreased-male, paroniria, thinking abnormal

REPRODUCTIVE: Female: leukorrhea, menstrual disorder;
Male: balanoposthitis

RESPIRATORY: dyspnea, rhinitis, sinusitis, bronchospasm, coughing, epistaxis, respiratory insufficiency, upper respiratory tract infection, respiratory disorder, asthma, hemoptysis, hypoxia, stridor

SKIN/APPENDAGES: pruritus, pruritus ani, skin disorder, skin ulceration, angioedema, dermatitis, dermatitis fungal, photosensitivity skin reaction, seborrhea, skin exfoliation, urticaria

SPECIAL SENSES: taste perversion, eye pain, abnormal vision, conjunctivitis, photophobia, conjuctival hemorrhage, hyperacusis, scotoma, tinnitus, visual field defect, diplopia, xerophthalmia

URINARY SYSTEM: dysuria, face edema, micturition frequency, nephritis interstitial, renal failure acute, renal function abnormal, urinary incontinence

LABORATORY CHANGES: Changes in laboratory parameters, without regard to drug relationship, occurring in ≥1% of TROVAN treated patients were: Decreased hemoglobin and hematocrit; increased platelets; decreased and increased WBC; eosinophilia; increased ALT (SGPT), AST (SGOT), and alkaline phosphatase; decreased protein and albumin; increased BUN and creatinine; decreased sodium; and bicarbonate. It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

The incidence and magnitude of liver function abnormalities with TROVAN were the same as comparator agents except in the only study in which oral TROVAN was administered for 28 days. In this study (chronic bacterial prostatitis) nine percent (13/140) of TROVAN-treated patients experienced elevations of serum transaminases (AST and/or ALT) of ≥3 times the upper limit of normal. These liver function test abnormalities generally developed at the end of, or following completion of, the planned 28-day course of therapy, but were not associated with concurrent elevations of related laboratory measures of hepatic function (such as serum bilirubin, alkaline phosphatase, or lactate dehydrogenase). Patients were asymptomatic with these abnormalities, which generally returned to normal within 1-2 months after discontinuation of therapy. (See **PRECAUTIONS - General.**)

OVERDOSAGE

Trovafloxacin has a low order of acute toxicity. The minimum lethal oral dose in mice and rats was 2000 mg/kg or greater. The minimum lethal i.v. dose for the prodrug, alatrofloxacin, was 50-125 mg/kg for mice and greater than 75 mg/kg for rats. Clinical signs observed included decreased activity and respiration, ataxia, ptosis, tremors and convulsions.

In the event of acute oral overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given symptomatic and supportive treatment. Adequate hydration should be maintained. Trovafloxacin is not efficiently removed from the body by hemodialysis.

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DOSAGE GUIDELINES		
INFECTION*/LOCATION AND TYPE	DAILY UNIT DOSE AND ROUTE OF ADMINISTRATION	TOTAL DURATION
Nosocomial Pneumonia (See NOTE 1 below)	300 mg I.V. followed by 200 mg oral	10-14 days
Community Acquired Pneumonia	200 mg oral or 200 mg I.V. followed by 200 mg oral	7-14 days
Acute Bacterial Exacerbation of Chronic Bronchitis	100 mg oral	7-10 days
Acute Sinusitis	200 mg oral	10 days
Complicated Intra-Abdominal Infections, including post-surgical infections	300 mg I.V. followed by 200 mg oral	7-14 days
Gynecologic and Pelvic Infections	300 mg I.V. followed by 200 mg oral	7-14 days
Surgical Prophylaxis - Elective Colorectal Surgery (See NOTE 2 below.)	200 mg I.V. or oral	Single intravenous or oral dose within 30 min. to 4 hours before surgery
Surgical Prophylaxis - Elective Abdominal and Vaginal Hysterectomy (See NOTE 2 below)	200 mg I.V. or oral	Single intravenous or oral dose within 30 min. to 4 hours before surgery
Skin and Skin Structure Infections, Uncomplicated	100 mg Oral	7-10 days
Skin and Skin Structure Infections, Complicated, including diabetic foot infections	200 mg oral or 200 mg I.V. followed by 200 mg oral	10-14 days
Uncomplicated Urinary Tract Infections (cystitis)	100 mg oral	3 days
Chronic Bacterial Prostatitis	200 mg oral	28 days
Uncomplicated Urethral Gonorrhea Males, Endocervical and Rectal Gonorrhea in Females	100 mg oral	Single Dose
Cervicitis due to *Chlamydia trachomatis*	200 mg oral	5 days
Pelvic Inflammatory Disease (mild to moderate)	200 mg oral	14 days

970 * due to the designated pathogens (See **INDICATIONS AND USAGE**)
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973 NOTE 1: As with other antimicrobials, where *Pseudomonas aeruginosa* is a documented or
974 presumptive pathogen, combination therapy with either an aminoglycoside or aztreonam
975 may be clinically indicated.
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977 NOTE 2: In patients where surgical prophylaxis with oral TROVAN is indicated, Bicitra®
978 should not be given within 2 hours. (See **PRECAUTIONS: Drug Interactions**)
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980 The safety and efficacy of TROVAN use for >4 weeks have not been studied. (See
981 **PRECAUTIONS.**)
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983 **IMPAIRED RENAL FUNCTION**: No adjustment in the dosage of TROVAN is necessary in
984 patients with impaired renal function. Trovafloxacin is eliminated primarily by biliary
985 excretion. Trovafloxacin is not efficiently removed from the body by hemodialysis.
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CHRONIC HEPATIC DISEASE (cirrhosis): The following table provides dosing guidelines for patients with mild or moderate cirrhosis (Child-Pugh Class A and B). There are no data in patients with severe cirrhosis (Child-Pugh Class C).

INDICATED DOSE (Normal hepatic function)	CHRONIC HEPATIC DISEASE DOSE
300 mg i.v.	200 mg i.v.
200 mg i.v. or oral	100 mg i.v. or oral.
100 mg oral	100 mg oral

INTRAVENOUS ADMINISTRATION

AFTER DILUTION WITH AN APPROPRIATE DILUENT TROVAN I.V. SHOULD BE ADMINISTERED BY INTRAVENOUS INFUSION OVER A PERIOD OF 60 MINUTES.

CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION SHOULD BE AVOIDED.

TROVAN I.V. is supplied in single-use vials containing a concentrated solution of alatrofloxacin mesylate in Water for Injection (equivalent of 200 mg or 300 mg as trovafloxacin). Each mL contains alatrofloxacin mesylate equivalent to 5 mg trovafloxacin. (See **HOW SUPPLIED** for container sizes.) THESE TROVAN I.V. SINGLE-USE VIALS MUST BE FURTHER DILUTED WITH AN APPROPRIATE SOLUTION PRIOR TO INTRAVENOUS ADMINISTRATION. This parenteral drug product should be inspected visually for discoloration and particulate matter prior to dilution and administration. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final parenteral solution.

PREPARATION OF ALATROFLOXACIN MESYLATE INJECTION FOR ADMINISTRATION

The intravenous dose should be prepared by aseptically withdrawing the appropriate volume of concentrate from the vials of TROVAN I.V. This should be diluted with a suitable intravenous solution to a final concentration of 1-2 mg/mL. (See **Compatible Intravenous Solutions**.) The resulting solution should be infused over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place.

Since the vials are for single-use only, any unused portion should be discarded.

Since only limited data are available on the compatibility of alatrofloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to TROVAN I.V. in single-use vials or infused simultaneously through the same intravenous line.

If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of TROVAN I.V. with an infusion solution compatible with TROVAN I.V. and with any other drug(s) administered via this common line.

If TROVAN I.V. is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

The desired dosage of TROVAN I.V. may be prepared according to the following chart:

DOSAGE STRENGTH (mg) (trovafloxacin equivalent)	VOLUME TO WITHDRAW (mL)	DILUENT VOLUME (mL)	TOTAL VOLUME (mL)	INFUSION CONC (mg/mL)
100 mg	20	30	50	2
100 mg	20	80	100	1
200 mg	40	60	100	2
200 mg	40	160	200	1
300 mg	60	90	150	2
300 mg	60	240	300	1

For example, to prepare a 200 mg dose at an infusion concentration of 2 mg/mL (as trovafloxacin), 40 mL of TROVAN I.V. is withdrawn from a vial and diluted with 60 mL of a compatible intravenous fluid to produce a total infusion solution volume of 100 mL.

Compatible Intravenous Solutions:

5% Dextrose Injection, USP
0.45% Sodium Chloride Injection, USP
5% Dextrose and 0.45% Sodium Chloride Injection, USP
5% Dextrose and 0.2% Sodium Chloride Injection, USP
Lactated Ringer's and 5% Dextrose Injection, USP

Stability of TROVAN I.V. as supplied:
When stored under recommended conditions, TROVAN I.V., as supplied in ~~(20 mL)~~ 40 mL or 60 mL vials, is stable through the expiration date printed on the label.

Stability of TROVAN I.V. Following Dilution:
TROVAN I.V., when diluted with the following intravenous solutions to concentrations of 0.5 to 2.0 mg/mL (as trovafloxacin), is physically and chemically stable for up to 7 days when refrigerated or up to 3 days at room temperature stored in glass bottles or plastic (PVC type) intravenous containers.

HOW SUPPLIED

Tablets
TROVAN (trovafloxacin mesylate) Tablets are available as blue, film-coated tablets. The 100 mg tablets are round and contain trovafloxacin mesylate equivalent to 100 mg trovafloxacin. The 200 mg tablets are modified oval-shaped and contain trovafloxacin mesylate equivalent to 200 mg trovafloxacin.

TROVAN Tablets are packaged and in unit dose blister strips in the following configurations:

100-mg tablets: color: blue; shape: round
debossing: "PFIZER" on side 1 and "378" on side 2
Bottles of 30 (NDC 0049-3780-30)
Unit Dose/ 40 tablets (NDC 0049-3780-43)

200-mg tablets: color: blue; shape: modified oval
debossing: "PFIZER" on side 1 and "379" on side 2
Bottles of 30 (NDC 0049-3790-30)
Unit Dose/ 40 tablets (NDC 0049-3790-43)

Storage
TROVAN Tablets should be stored at 15 °C to 30 °C (59 °F to 86 °F) in well-closed containers.

Injection
TROVAN is also available for intravenous administration as the prodrug, TROVAN I.V. (alatrofloxacin mesylate injection), in the following configurations:
Single-use vials containing a clear, colorless to pale-yellow concentrated solution of alatrofloxacin mesylate equivalent to 5 mg trovafloxacin/mL.

5 mg/mL, 40 mL, 200 mg
Unit dose package (NDC 0049-3890-28)

5 mg/mL, 60 mL, 300 mg
Unit dose package (NDC 0049-3900-28)

Storage
TROVAN I.V. should be stored at 15 °C to 30 °C (59 °F to 86 °F). Protect From Light. Do Not Freeze.

ANIMAL PHARMACOLOGY:

Quinolones have been shown to cause arthropathy in immature animals.

Arthropathy and chondrodysplasia were observed in immature animals given trovafloxacin (See **WARNINGS**).

At doses from 10 to 15 times the human dose base on a mg/kg or approximately 3 to 5 times based on mg/m^2, trovafloxacin has been shown to cause arthropathy in immature rats and dogs. In addition, these drugs are associated with an increased incidence of chondrodysplasia in rats compared to controls. There is no evidence of arthropathies in fully mature rats and dogs at doses from 40 or 10 times the human dose based on mg/kg or approximately 5 times based on mg/m^2 for a 6 month exposure period.

Unlike some other members of the quinolone class, crystalluria and ocular toxicity were not observed in chronic safety studies with rats or dogs with either trovafloxacin or its prodrug, alatrofloxacin.

Quinolones have been reported to have proconvulsant activity that is exacerbated with concomitant use of non-steroidal antiinflammatory drugs (NSAIDS). Neither trovafloxacin administered orally at 500 mg/kg, nor alatrofloxacin administered intravenously at 75 mg/kg, showed an increase in measures of seizure activity in mice at doses when used in combination with the active metabolite of the NSAID, fenbufen.

As with other members of the quinolone class, trovafloxacin at doses 5 to 10 times the human dose based on mg/kg or 1 to 5 times the human dose based on mg/m^2 produces testicular degeneration in rats and dogs dosed for 6 months.

At a dose of trovafloxacin 10 times the highest human dose based on mg/kg or approximately 5 times based on mg/m^2, elevated liver enzyme levels which correlated with centrilobar hepatocellular vacuolar degeneration and necrosis were observed in dogs in a 6 month study. A subsequent study demonstrated reversibility of these effects when trovafloxacin was discontinued.

CLINICAL STUDIES

Acute Bacterial Exacerbation of Chronic Bronchitis

Patients with clinically documented acute bacterial exacerbation of chronic bronchitis participated in a randomized, double blind, multicenter trial comparing oral trovafloxacin (100mg once daily) with oral clarithromycin (500mg twice daily) for 7 days. The clinical success rate (cure + improvement, with no need for further antibiotic therapy) at the End of Treatment was 89% (181/203) and 85% (160/188) for trovafloxacin and clarithromycin respectively. The clinical success rate at the End of Study (Day 28) was 80% (158/197) and 74% (131/178) for trovafloxacin and clarithromycin respectively.

The following are the clinical success rates for the clinically evaluable groups by pathogen:

	End of Treatment		End of Study	
Pathogen	Trovafloxacin 100 mg	Clarithromycin 500 mg BID	Trovafloxacin 100 mg	Clarithromycin 500 mg BID
H. influenzae	92% (24/26)	89% (16/18)	92% (24/26)	44% (7/16)*
M. catarrhalis	78% (14/18)	80% (16/20)	71% (12/17)	74% (14/19)
S. pneumoniae	100% (7/7)	91% (10/11)	86% (6/7)	91% (10/11)
H. parainfluenzae	100% (6/6)	86% (6/7)	100% (6/6)	86% (6/7)
S.aureus	93% (13/14)	83% (10/12)	85% (11/13)	75% (9/12)

*p= 0.001

Of the above patients with clinical failure at end of treatment or study, no trovafloxacin and 2 clarithromycin patients (both *H.influenzae*) had positive post treatment cultures for the baseline pathogen. There was no emergence of resistance in either treatment group. Fewer patients required hospitalization during study (Day 1-35) in the trovafloxacin group (3/210) than in the clarithromycin group (10/200), p=0.039.

Hospitalized Community Acquired Pneumonia

Adult patients with clinically and radiologically documented community acquired pneumonia, requiring hospitalization and initial intravenous therapy, participated in two randomized, multicenter, double-blind, double-dummy trials. The first trial compared intravenous alatrofloxacin (200mg once daily for 2 to 7 days) followed by oral trovafloxacin (200mg once daily) for a total of 7 to 14 days of therapy to intravenous ciprofloxacin (400mg BID) plus ampicillin (500mg QID) for 2 to 7 days followed by oral ciprofloxacin (500mg BID) plus amoxicillin (500mg TID) for a total of 7 to 14 days of therapy. The second study compared intravenous alatrofloxacin (200mg once daily for 2 to 7 days) followed by oral trovafloxacin (200mg once daily) for a total of 7 to 14 days of therapy to intravenous ceftriaxone (1000mg once daily for 2 to 7 days) followed by oral cefpodoxime (400mg BID) for 7 to 14 days of total therapy with optional blinded erythromycin added to the ceftriaxone/cefpodoxime arm if an atypical pneumonia was suspected.

The clinical success rate (cure + improvement with no need for further antibiotic therapy) at the End of Treatment was 90% (311/346) and 90% (325/363) for TROVAN and the comparator agents respectively. The clinical success rate at the End of Study (Day 30) was 86% (256/299) and 85% (283/334) for TROVAN and the comparator agents respectively. All cause mortality (Day 1-35) was 2.45% (10/408) on TROVAN and 5.45% (23/422) on the comparator agents.

The following outcomes are the clinical success rates for the clinically evaluable patient groups by pathogen in these two studies:

	End of Treatment		End of Study	
Pathogen	TROVAN	Comparators	TROVAN	Comparators
S. pneumoniae	89% (63/71)	95% (62/65)	87% (55/63)	91% (50/55)
H. influenzae	97% (35/36)	94% (46/49)	90% (28/31)	94% (44/47)
M. catarrhalis	100% (8/8)	100% (4/4)	100% (6/6)	100% (4/4)
S. aureus	100% (8/8)	93% (13/14)	100% (6/6)	91% (10/11)
K. pneumoniae	100% (3/3)	89% (8/9)	100% (3/3)	86% (6/7)
L. pneumophila	77% (10/13)	86% (12/14)	75% (9/12)	86% (12/14)
M. pneumoniae	100% (20/20)	87% (13/15)	94% (17/18)	79% (11/14)
C. pneumoniae	75% (6/8)	100% (18/18)	67% (4/6)	94% (16/17)

Of the above patients with clinical failure at end of treatment or study, only one alatrofloxacin patient (*H. influenzae + S .pneumoniae*) and one ceftriaxone + erythromycin patient (*Legionella*) had a microbiologically confirmed persistent pathogen at the time of failure with no emergence of resistance in either study.

Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia, participated in a randomized, multicenter, double-blind, double-dummy trial comparing intravenous alatrofloxacin (300mg once daily for 2 to 7 days) followed by oral trovafloxacin (200mg once daily) for a total of 7 to 14 days of therapy to intravenous ciprofloxacin (400mg BID) for 2 to 7 days followed by oral ciprofloxacin (750mg BID) for a total of 7 to 14 days of therapy with optional blinded clindamycin or metronidazole added to the ciprofloxacin arm if an anaerobic pneumonia was suspected. In subjects with documented Pseudomonas infection or methicillin-resistant S. aureus, aztreonam or vancomycin, respectively, could have been added to either treatment regimen.

The clinical success rate (cure + improvement with no need for further antibiotic therapy) at the End of Treatment was 77% (68/88) and 78% (79/101) for TROVAN and ciprofloxacin respectively. The clinical success rate at the End of Study (Day 30) was 69% (50/72) and 68% (54/79) for TROVAN and ciprofloxacin respectively.

The following outcomes are the clinical success rates for the clinically evaluable patient groups by pathogen:

	End of Treatment		End of Study	
Pathogen	TROVAN	Ciprofloxacin	TROVAN	Ciprofloxacin
P. aeruginosa	67% (10/15)	55% (6/11)	62% (8/13)	25% (2/8)
H. influenzae	88% (7/8)	89% (8/9)	83% (5/6)	86% (6/7)
E. coli	71% (5/7)	80% (4/5)	50% (3/6)	80% (4/5)
S. aureus	64% (7/11)	80% (8/10)	50% (4/8)	67% (4/6)

Of the above patients with clinical failure at end of treatment or study, two alatrofloxacin patients (*S.aureus, P.aeruginosa*) and 4 ciprofloxacin patients (all *P.aeruginosa*) had a microbiologically confirmed persistent pathogen at the time of failure. Three of the 4 ciprofloxacin patients with clinical failure and persistence had emergence of resistance with none on alatrofloxacin.

Complicated Intra-Abdominal Infections

Patients hospitalized with clinically-documented, complicated intra-abdominal infections, including post-surgical infections participated in a randomized, double-blind, multicenter trial comparing intravenous alatrofloxacin (300 mg once daily) followed by oral trovafloxacin (200 mg once daily) to intravenous imipenem/cilastatin (1g q8h) followed by oral amoxicillin/clavulanic acid (500 mg TID) for a maximum of 14 days of therapy. The clinical success rate (cure + improvement) at the End of Treatment was 88% (136/155) and 86% (122/142) for alatrofloxacin→trovafloxacin and imipenem/cilastatin→amoxicillin/clavulanic acid, respectively. The clinical success rate at the End of Study (Day 30) was 83% (129/156) and 84% (127/152) for alatrofloxacin→trovafloxacin and imipenem/cilastatin→amoxicillin/clavulanic acid respectively.

The following are the clinical success rates for the clinically-evaluable patient groups by pathogen:

	End of Treatment		End of Study	
Pathogen	TROVAN	Imipenem/Cila Amox/Clav	TROVAN	Imipenem/Cila Amox/Clav
E. coli	94% (72/77)	90% (52/58)	86% (66/77)	86% (51/59)

Bacteroides fragilis	97% (30/31)	82% (28/34)	84% (26/31)	75% (27/36)
viridans group streptococci	90% (18/20)	83% (19/23)	90% (18/20)	78% (18/23)
Pseudomonas aeruginosa	94% (15/16)	82% (14/17)	88% (14/16)	83% (15/18)
Klebsiella pneumoniae	80% (12/15)	71% (10/14)	67% (10/15)	71% (10/14)
Peptostreptococcus spp.	86% (12/14)	88% (7/8)	79% (11/14)	75% (6/8)
Prevotella spp.	77% (10/13)	50% (2/4)	77% (10/13)	60% (3/5)

Of patients with a baseline pathogen and a clinical response of failure at the End of Study, 9 of 26 on TROVAN and 10 of 21 on imipenem/cilastatin had microbiologically-confirmed persistence of the baseline pathogen with no emergence of resistance in either group.

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REFERENCES:

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